

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of

Tsuyoshi Maekawa

Serial No. 10/517,214

Group Art Unit 1624

Filed March 1, 2005

Examiner JAISLE, CECILIA M

For : 1,2-AZOLE DERIVATIVES WITH HYPOGLYCEMIC AND  
HYPOLIPIDEMIC ACTIVITY

**TRANSLATOR'S DECLARATION**

Honorable Commissioner of Patents and Trademarks

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

I, Ritsuko Arimura, declare:

That I am well acquainted with both the Japanese and English languages;

That the attached document represents a true English translation of Japanese Patent Application No. 2003-016748 (filing date January 24, 2003); and

That I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 11th day of December, 2008.

.....  
Ritsuko Arimura

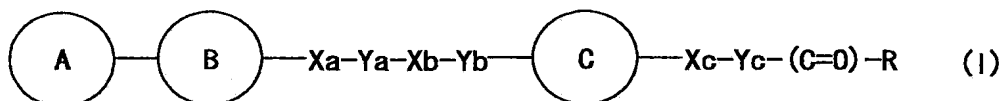
【Document】 SPECIFICATION

【Title of the Invention】 1,2-Azole Derivative

【What is Claimed is】

【Claim 1】 A compound represented by the formula

5



wherein

ring A is a ring optionally having 1 to 3 substituents;

10 ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

15 are the same or different and each is a bond, -O-,  
-S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>-  
or -NR<sup>3</sup>CO- (R<sup>1</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group, R<sup>2</sup> is a hydrogen atom or  
a hydroxy-protecting group, R<sup>3</sup> is a hydrogen atom, an  
optionally substituted hydrocarbon group or an amino-  
protecting group);

20 Ya is a divalent aliphatic hydrocarbon residue having 1  
to 20 carbon atoms;

Yb and Yc

are the same or different and each is a bond or a  
divalent aliphatic hydrocarbon residue having 1 to 20  
carbon atoms;

25 ring C is a monocyclic aromatic ring optionally further  
having 1 to 3 substituents;

30 R represents -OR<sup>4</sup> (R<sup>4</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group) or -NR<sup>5</sup>R<sup>6</sup> (R<sup>5</sup> and R<sup>6</sup> are  
the same or different and each is a hydrogen atom, an  
optionally substituted hydrocarbon group or an  
optionally substituted heterocyclic group, or R<sup>5</sup> and R<sup>6</sup>  
form, together with the adjacent nitrogen atom, an  
optionally substituted heterocyclic ring),

provided that,

(1) when the 1,2-azole ring represented by ring B is pyrazole, ring C is not thiadiazole or oxadiazole;

5 (2) when the 1,2-azole ring represented by ring B is isoxazole, ring C is not an optionally substituted pyridone; and

(3) when the 1,2-azole ring represented by ring B is pyrazole and Xa and Xb are each a bond, ring C is not a benzene ring,

10 or a salt thereof or a prodrug thereof.

【claim 2】 The compound of claim 1, wherein the ring represented by ring A is an aromatic ring.

【claim 3】 The compound of claim 2, wherein the aromatic ring is a benzene ring or a pyridine ring.

15 【claim 4】 The compound of claim 1, wherein the 1,2-azole ring represented by ring B is pyrazole.

【claim 5】 The compound of claim 1, wherein the substituent that ring B is optionally further having is a hydrocarbon group.

20 【claim 6】 The compound of claim 1, wherein the substituent that ring B is optionally further having is an alkoxy group.

【claim 7】 The compound of claim 1, wherein Ya is C<sub>1-6</sub> alkylene or C<sub>2-6</sub> alkenylene.

25 【claim 8】 The compound of claim 1, wherein Xb is -O-, -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>- or -NR<sup>3</sup>CO- (R<sup>1</sup> is a hydrogen atom or an optionally substituted hydrocarbon group, R<sup>2</sup> is a hydrogen atom or a hydroxy-protecting group, and R<sup>3</sup> is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group).

30 【claim 9】 The compound of claim 1, wherein the monocyclic aromatic ring represented by ring C is a benzene ring.

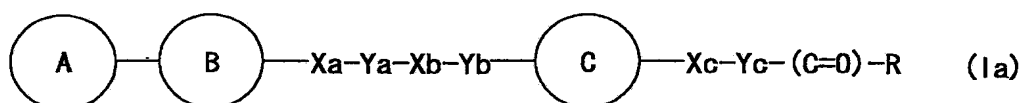
【claim 10】 The compound of claim 1, wherein the monocyclic aromatic ring represented by ring C is pyrazole.

35 【claim 11】 The compound of claim 1, wherein R represents -OR<sup>4</sup> (R<sup>4</sup> is a hydrogen atom or an optionally substituted hydrocarbon

group).

[claim 12] A pharmaceutical composition comprising the compound of claim 1 or a salt thereof or a prodrug thereof.

[claim 13] An agent for the prophylaxis or treatment of diabetes, which comprises a compound represented by the formula



wherein

ring A is a ring optionally having 1 to 3 substituents;

ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

are the same or different and each is a bond, -O-,  
-S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>-  
or -NR<sup>3</sup>CO- (R<sup>1</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group, R<sup>2</sup> is a hydrogen atom or  
a hydroxy-protecting group, R<sup>3</sup> is a hydrogen atom, an  
optionally substituted hydrocarbon group or an amino-  
protecting group);

Ya is a divalent aliphatic hydrocarbon residue having 1  
to 20 carbon atoms;

Yb and Yc

are the same or different and each is a bond or a  
divalent aliphatic hydrocarbon residue having 1 to 20  
carbon atoms;

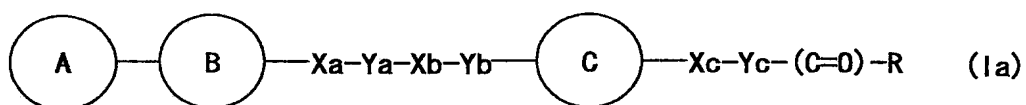
ring C is a monocyclic aromatic ring optionally further  
having 1 to 3 substituents;

R represents -OR<sup>4</sup> (R<sup>4</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group) or -NR<sup>5</sup>R<sup>6</sup> (R<sup>5</sup> and R<sup>6</sup> are  
the same or different and each is a hydrogen atom, an  
optionally substituted hydrocarbon group or an  
optionally substituted heterocyclic group, or R<sup>5</sup> and R<sup>6</sup>



form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring), or a salt thereof or a prodrug thereof.

5    **[claim 14]** An agent for the prophylaxis or treatment of hyperlipidemia, which comprises a compound represented by the formula



wherein

10    ring A is a ring optionally having 1 to 3 substituents;

ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

15    are the same or different and each is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>- or -NR<sup>3</sup>CO- (R<sup>1</sup> is a hydrogen atom or an optionally substituted hydrocarbon group, R<sup>2</sup> is a hydrogen atom or a hydroxy-protecting group, R<sup>3</sup> is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

20    Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

Yb and Yc

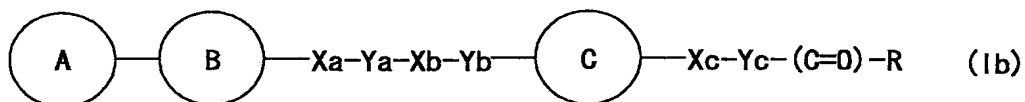
25    are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents;

30    R represents -OR<sup>4</sup> (R<sup>4</sup> is a hydrogen atom or an optionally substituted hydrocarbon group) or -NR<sup>5</sup>R<sup>6</sup> (R<sup>5</sup> and R<sup>6</sup> are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R<sup>5</sup> and R<sup>6</sup>

form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring), or a salt thereof or a prodrug thereof.

5    [claim 15] An agent for the prophylaxis or treatment of arteriosclerosis, which comprises a compound represented by the formula



wherein

10    ring A    is a ring optionally having 1 to 3 substituents;  
      ring B    is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

15            are the same or different and each is a bond, -O-,  
             -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>-  
             or -NR<sup>3</sup>CO- (R<sup>1</sup> is a hydrogen atom or an optionally  
             substituted hydrocarbon group, R<sup>2</sup> is a hydrogen atom or  
             a hydroxy-protecting group, and R<sup>3</sup> is a hydrogen atom,  
20            an optionally substituted hydrocarbon group or an  
             amino-protecting group);

Ya           is a divalent aliphatic hydrocarbon residue having 1  
             to 20 carbon atoms;

Yb and Yc

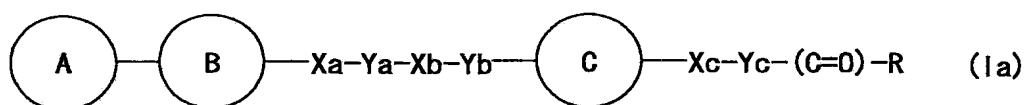
25            are the same or different and each is a bond or a  
             divalent aliphatic hydrocarbon residue having 1 to 20  
             carbon atoms;

ring C       is a monocyclic aromatic ring optionally further  
             having 1 to 3 substituents;

30            R       represents -OR<sup>4</sup> (R<sup>4</sup> is a hydrogen atom or an optionally  
                     substituted hydrocarbon group) or -NR<sup>5</sup>R<sup>6</sup> (R<sup>5</sup> and R<sup>6</sup> are  
                     the same or different and each is a hydrogen atom, an  
                     optionally substituted hydrocarbon group or an  
                     optionally substituted heterocyclic group, or R<sup>5</sup> and R<sup>6</sup>

form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring), provided that, when the 1,2-azole ring represented by ring B is isoxazole, ring C is not an optionally substituted pyridone,  
5 or a salt thereof or a prodrug thereof.

10 [claim 16] An agent for the prophylaxis or treatment of impaired glucose tolerance, which comprises a compound represented by the formula



wherein  
ring A is a ring optionally having 1 to 3 substituents;  
ring B is a 1,2-azole ring optionally further having 1 to 3  
15 substituents;

Xa, Xb and Xc  
are the same or different and each is a bond, -O-,  
-S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>-  
or -NR<sup>3</sup>CO- (R<sup>1</sup> is a hydrogen atom or an optionally  
20 substituted hydrocarbon group, R<sup>2</sup> is a hydrogen atom or  
a hydroxy-protecting group, R<sup>3</sup> is a hydrogen atom, an  
optionally substituted hydrocarbon group or an amino-  
protecting group);

Ya is a divalent aliphatic hydrocarbon residue having 1  
25 to 20 carbon atoms;

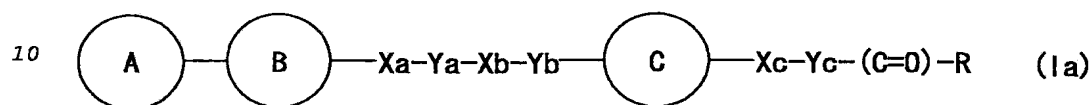
Yb and Yc  
are the same or different and each is a bond or a  
divalent aliphatic hydrocarbon residue having 1 to 20  
carbon atoms;

30 ring C is a monocyclic aromatic ring optionally further  
having 1 to 3 substituents;

R represents -OR<sup>4</sup> (R<sup>4</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group) or -NR<sup>5</sup>R<sup>6</sup> (R<sup>5</sup> and R<sup>6</sup> are

the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R<sup>5</sup> and R<sup>6</sup> form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring),  
or a salt thereof or a prodrug thereof.

【claim 17】 A retinoid-related receptor function regulating agent, which comprises a compound represented by the formula



wherein

ring A is a ring optionally having 1 to 3 substituents;

ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

15 Xa, Xb and Xc

are the same or different and each is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>- or -NR<sup>3</sup>CO- (R<sup>1</sup> is a hydrogen atom or an optionally substituted hydrocarbon group, R<sup>2</sup> is a hydrogen atom or a hydroxy-protecting group, R<sup>3</sup> is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

25 Yb and Yc

are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents;

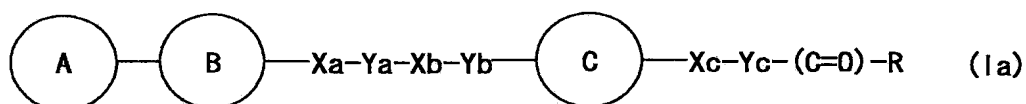
R represents -OR<sup>4</sup> (R<sup>4</sup> is a hydrogen atom or an optionally substituted hydrocarbon group) or -NR<sup>5</sup>R<sup>6</sup> (R<sup>5</sup> and R<sup>6</sup> are the same or different and each is a hydrogen atom, an

optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R<sup>5</sup> and R<sup>6</sup> form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring),  
5 or a salt thereof or a prodrug thereof.

【claim 18】 The agent of claim 17, which is a peroxisome proliferator-activated receptor ligand.

【claim 19】 The agent of claim 17, which is a retinoid X receptor ligand.

10 【claim 20】 An insulin resistance improving agent, which comprises a compound represented by the formula



wherein

15 ring A is a ring optionally having 1 to 3 substituents;  
ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

are the same or different and each is a bond, -O-,  
20 -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>-  
or -NR<sup>3</sup>CO- (R<sup>1</sup> is a hydrogen atom or an optionally substituted hydrocarbon group, R<sup>2</sup> is a hydrogen atom or a hydroxy-protecting group, R<sup>3</sup> is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);  
25

Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

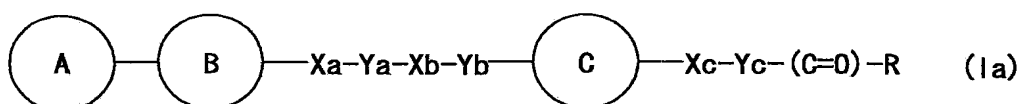
Yb and Yc

are the same or different and each is a bond or a  
30 divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents;

R represents  $-OR^4$  ( $R^4$  is a hydrogen atom or an optionally substituted hydrocarbon group) or  $-NR^5R^6$  ( $R^5$  and  $R^6$  are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or  $R^5$  and  $R^6$  form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring), or a salt thereof or a prodrug thereof.

5  
10  
[claim 21] A method for the prophylaxis or treatment of diabetes in a mammal, which comprises administering a compound represented by the formula



wherein

15 ring A is a ring optionally having 1 to 3 substituents;  
ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

are the same or different and each is a bond, -O-,  
20 -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>-  
or -NR<sup>3</sup>CO- ( $R^1$  is a hydrogen atom or an optionally substituted hydrocarbon group,  $R^2$  is a hydrogen atom or a hydroxy-protecting group,  $R^3$  is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

25 Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

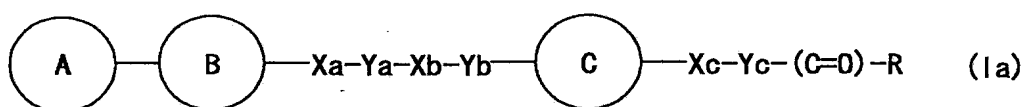
Yb and Yc

are the same or different and each is a bond or a  
30 divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents;

R represents  $-OR^4$  ( $R^4$  is a hydrogen atom or an optionally substituted hydrocarbon group) or  $-NR^5R^6$  ( $R^5$  and  $R^6$  are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or  $R^5$  and  $R^6$  form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring), or a salt thereof or a prodrug thereof to the mammal.

[claim 22] Use of a compound represented by the formula



wherein

ring A is a ring optionally having 1 to 3 substituents;

ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

are the same or different and each is a bond,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$ ,  $-CO-$ ,  $-CS-$ ,  $-CR^1(OR^2)-$ ,  $-NR^3-$ ,  $-CONR^3-$  or  $-NR^3CO-$  ( $R^1$  is a hydrogen atom or an optionally substituted hydrocarbon group,  $R^2$  is a hydrogen atom or a hydroxy-protecting group,  $R^3$  is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

Yb and Yc

are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents;

R represents  $-OR^4$  ( $R^4$  is a hydrogen atom or an optionally substituted hydrocarbon group) or  $-NR^5R^6$  ( $R^5$  and  $R^6$  are

the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R<sup>5</sup> and R<sup>6</sup> form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring), or a salt thereof or a prodrug thereof, for the production of an agent for the prophylaxis or treatment of diabetes mellitus.

#### 【Detailed Description of the Invention】

##### 【Technical Field to which the Invention pertains】

The present invention relates to a 1,2-azole derivative having an excellent hypoglycemic action and hypolipidemic action, which is useful as an agent for the prophylaxis or treatment of diabetes mellitus, hyperlipidemia, arteriosclerosis, impaired glucose tolerance and the like.

##### 【Prior Art】

Peroxisome proliferator-activated receptor gamma (PPAR<sub>γ</sub>), a member of the intranuclear hormone receptor superfamily, which is typically exemplified by steroid hormone receptors and thyroid hormone receptors, plays an important role as a master regulator in the differentiation of adipocytes with its expression induced in the very early stage of adipocyte differentiation. PPAR<sub>γ</sub> forms a dimer with the retinoid X receptor (RXR) by binding to a ligand, and binds to a responsive site of the target gene in the nucleus to directly control (activate) transcription efficiency. In recent years, the possibility that 15-deoxy-Δ<sup>12,14</sup> prostaglandin J<sub>2</sub>, a metabolite of prostaglandin D<sub>2</sub>, serves as an endogenous ligand for PPAR<sub>γ</sub>, has been suggested, and it has been shown that a class of insulin sensitivity enhancers, typically exemplified by thiazolidinedione derivatives, possess ligand activity for PPAR<sub>γ</sub>, and that its potency is proportional to its hypoglycemic action or adipocyte differentiation-promoting action (e.g., see non-patent references 1-3). Furthermore, in recent years, it has been shown that 1) PPAR<sub>γ</sub> is expressed in cultured cells



of human liposarcoma origin, whose proliferation is ceased by the addition of a PPAR $\gamma$  ligand (e.g., see non-patent reference 4), 2) nonsteroidal anti-inflammatory drugs, typically exemplified by indomethacin and fenoprofen, have PPAR $\gamma$  ligand activity (e.g., see non-patent reference 5), 3) PPAR $\gamma$  is expressed at high levels in activated macrophages, with the transcription of a gene involved in inflammation inhibited by the addition of a ligand therefor (e.g., see non-patent reference 6), 4) PPAR $\gamma$  ligands suppress the production of inflammatory cytokines (TNF $\alpha$ , IL-1 $\beta$ , IL-6) by monocytes (e.g., see non-patent reference 7), 5) hypertrophy of adipocyte, accumulation of lipid and expression of insulin resistance are suppressed in PPAR $\gamma$  hetero deficient mouse (e.g., see non-patent reference 8), 6) PPAR $\gamma$  ligand inhibits differentiation of 10T1/2 cells to adipocytes by PPAR $\gamma$  agonist (e.g., see non-patent reference 9), 7) PPAR $\gamma$  ligand suppresses differentiation of 3T3-L1 cells to adipocytes by PPAR $\gamma$  agonist (e.g., see non-patent reference 10) and the like.

**[0003]**

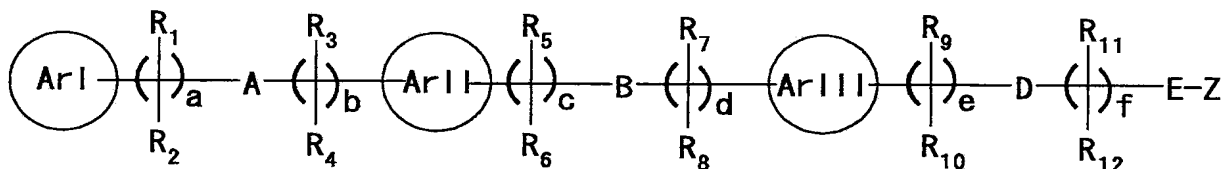
Peroxisome proliferator-activated receptor delta (PPAR $\delta$ ) is a member of the intranuclear hormone receptor PPAR family, forms a dimer with a retinoid X receptor (RXR) by ligand binding as in other PPAR families, and binds with a responsive element located upstream of the target gene in nucleus, thereby directly controlling transcription efficiency. As the ligand of PPAR $\delta$ , long chain fatty acids and carbaprostacyclin can be mentioned; however, a target gene specific to PPAR $\delta$  has not been identified as yet. PPAR $\delta$  shows ubiquitous expression, but shows particularly strong expression in gut, kidney and heart. As regards PPAR $\delta$ , it has been reported that PPAR $\delta$  shows differentiation-promoting effect on mouse preadipocytes (e.g., see non-patent references 11-13); it shows UCP-2 and UCP-3 expression-promoting effect on rat and human skeletal muscle cells (e.g., see non-patent references 14, 15); it shows differentiation-promoting effect on oligodendrocytes (e.g.,

see non-patent references 16, 17); it shows HDL-C increasing effect in db/db mouse (e.g., see non-patent reference 18); it shows HDL-C increasing effect and LDL-C, VLDL and TG-lowering effect in obesity Rhesus monkey; and it shows promoting effect on cholesterol transport of human monocyte THP-1 cells via ApoA1 (e.g., see non-patent reference 19). Moreover, it has been reported that PPAR $\delta$  is involved in colon cancer (e.g., see non-patent references 20, 21), embryo implantation during gestation (e.g., see non-patent reference 22), bone resorption in osteoclasts (e.g., see non-patent reference 23), apoptosis in inflammation (e.g., see non-patent reference 24), and regulation of type 2 acyl-CoA synthetase in brain (e.g., see non-patent reference 25).

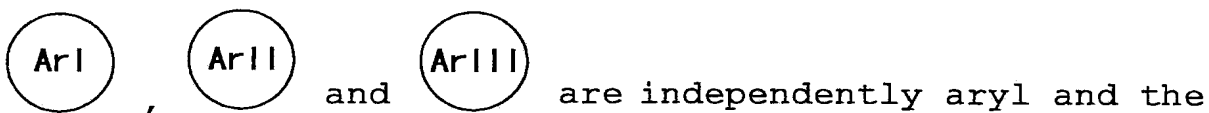
**[0004]**

As PPAR ligands, the following compounds are known.

(1) As a PPAR receptor ligand, a compound represented by the formula

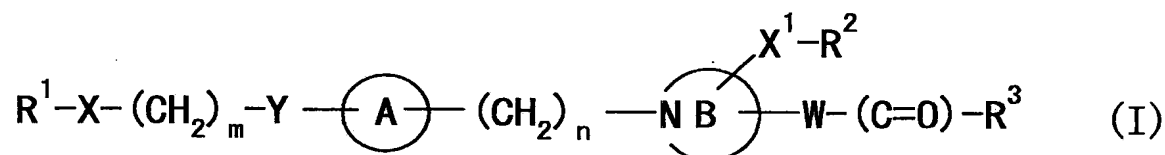


wherein



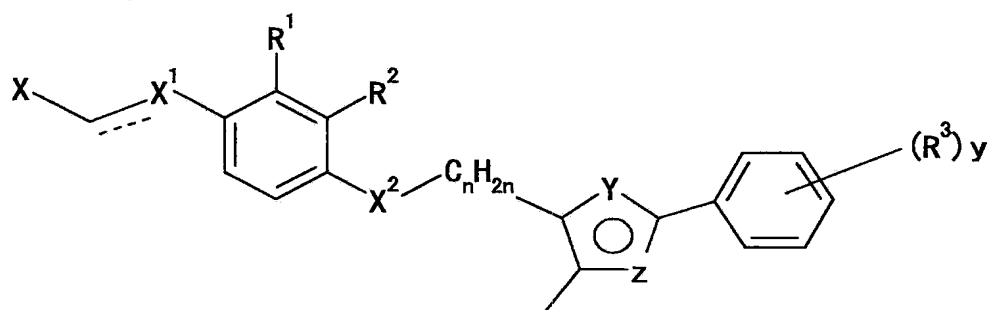
like; A is -O- and the like; B is -O- and the like; D is -O- and the like; E is a bond or ethylene group; a, b, c and e are each 0-4; d is 0-5; f is 0-6; R<sub>1</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>7</sub>, R<sub>9</sub> and R<sub>11</sub> are independently hydrogen and the like; R<sub>2</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>8</sub>, R<sub>10</sub> and R<sub>12</sub> are independently -(CH)<sub>q</sub>-X; q is 0-3; X is hydrogen and the like; Z is R<sub>21</sub>O<sub>2</sub>C- and the like; and R<sub>21</sub> is hydrogen and the like has been reported (see patent reference 1).

(2) As a retinoid-related receptor function regulator, a compound represented by the formula



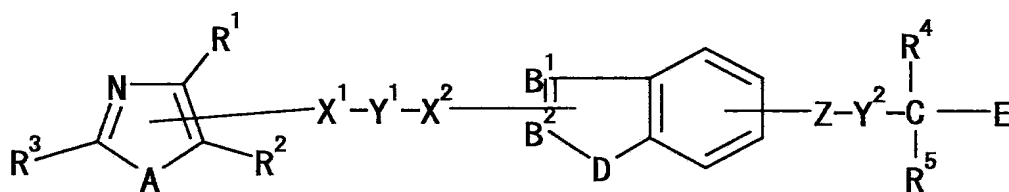
wherein  $R^1$  is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; X is a bond, O, S, -CO-, -CS-, -CR<sup>4</sup>(OR<sup>5</sup>)- or -NR<sup>6</sup>- ( $R^4$  and  $R^6$  are each a hydrogen atom or an optionally substituted hydrocarbon group,  $R^5$  is a hydrogen atom or a hydroxy-protecting group); m is 0-3; Y is O, S, -SO-, -SO<sub>2</sub>-, -NR<sup>7</sup>-, -CONR<sup>7</sup>- or -NR<sup>7</sup>CO- ( $R^7$  is a hydrogen atom or an optionally substituted hydrocarbon group); ring A is an aromatic ring which may further have 1 to 3 substituents; n is 1-8; ring B is a nitrogen-containing 5-membered heterocyclic ring which may be further substituted by alkyl group;  $X^1$  is a bond, O, S, -SO-, -SO<sub>2</sub>-, -O-SO<sub>2</sub>- or -NR<sup>16</sup>- ( $R^{16}$  is a hydrogen atom or an optionally substituted hydrocarbon group);  $R^2$  is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; W is a bond or a C1-20 divalent hydrocarbon residue; and  $R^3$  is -OR<sup>8</sup> ( $R^8$  is a hydrogen atom or an optionally substituted hydrocarbon group) or -NR<sup>9</sup>R<sup>10</sup> ( $R^9$  and  $R^{10}$  are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group or an optionally substituted acyl group, or  $R^9$  and  $R^{10}$  are bonded to each other to form a ring) has been reported (see patent reference 2).

(3) As a selective activator of human PPAR $\delta$ , a compound represented by the formula



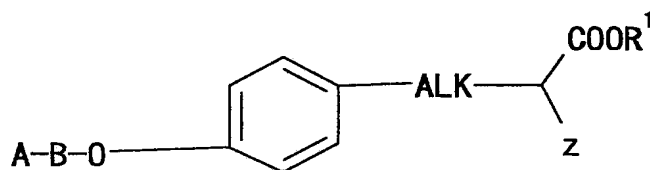
wherein X is COOH or a tetrazolyl group; X¹ is NH, NCH₃, O, S, a bond and the like; X² is O or S; R¹ and R² are independently H, CH₃, OCH₃ or a halogen; n is 1 or 2; one of Y and Z is N and the other is S or O; y is 0, 1, 2, 3, 4 or 5; and R³ is CF₃ or a halogen (see patent reference 3).

(4) As a PPARδ activator, a compound represented by the formula



wherein A is O, S and the like; R¹, R² and R³ are each a hydrogen atom, C1-8 alkyl, C6-10 aryl group which may have substituents and the like; X¹ and X² are O, S and the like; Y¹ is a C1-8 alkylene chain which may have substituents; B¹ is CW¹ (W¹ is a hydrogen atom and the like) or N; B² is CW² (W² is a hydrogen atom and the like) or N; D is O, S and the like; Z is O or S; Y² is a C1-4 alkylene chain or a bond; R⁴ and R⁵ are each a hydrogen atom and the like; and E is a carboxyl group, a C2-8 alkoxy carbonyl group and the like, has been reported (see patent reference 4).

(5) As a PPARγ agonist, a compound represented by the formula

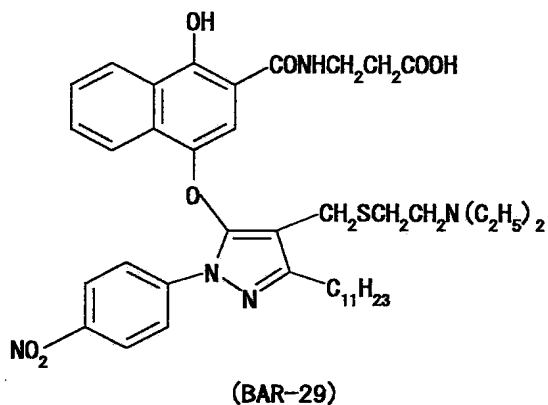
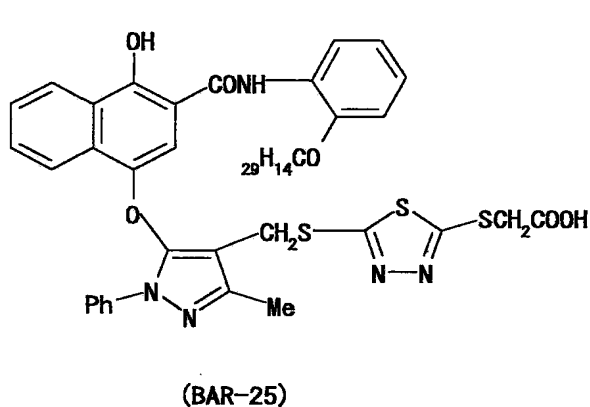


wherein A is a phenyl optionally substituted by a substituent

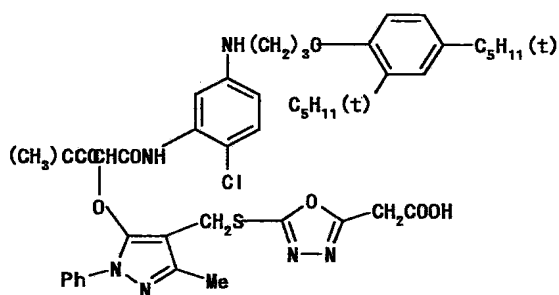
selected from a halogen atom, C1-6 alkyl, C1-3 alkoxy, C1-3 fluoroalkoxy and the like, a 5- or 6-membered heterocyclic group containing at least one heteroatom selected from O, N and S and the like; B is C1-6 alkylene, -MC1-6 alkylene (M is O, S and the like), a 5- or 6-membered heterocyclic group containing at least one nitrogen heteroatom and at least one heteroatom selected from O, N and S, which is optionally substituted by C1-3 alkyl, Het-C1-6 alkylene (Het is a heterocyclic group) and the like; ALK is C1-3 alkylene; R<sup>1</sup> is a hydrogen atom or C1-3 alkyl; Z is -(C1-3 alkylene)phenyl in which phenyl may be substituted by halogen atom and the like, has been reported (see patent reference 5).

In the meantime, as a 1,2-azole derivative, the following compounds are known.

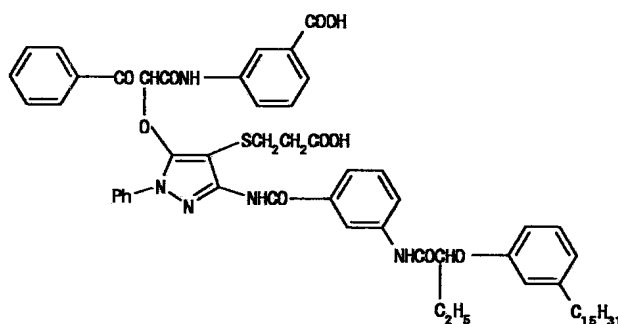
- (6) As a bleach accelerator releasing compound used for color photosensitive materials, the following compounds have been reported (see patent reference 6).



- (7) As a bleach accelerator releasing compound used for color photosensitive materials, the following compounds have been reported (see patent reference 7).

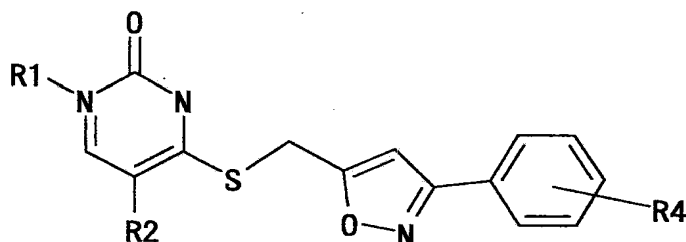


C-(10)



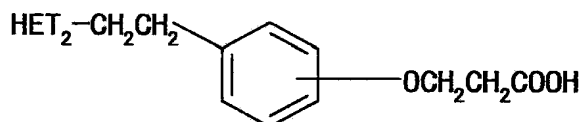
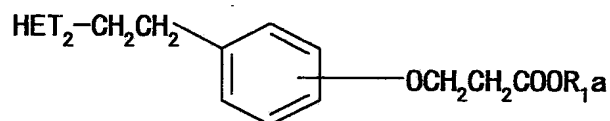
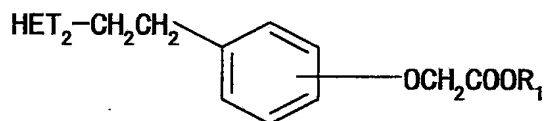
C-(42)

(8) As an endothelin converting enzyme inhibitor, a compound represented by the formula



wherein R<sub>1</sub> is C1-8 alkyl and the like which may be substituted by a substituent selected from halogen, nitro, cyano, -COOH, -COO-C1-3 alkyl and the like; R<sub>2</sub> is C1-5 alkyl and the like; R<sub>4</sub> is H and the like, has been reported (see patent reference 8).

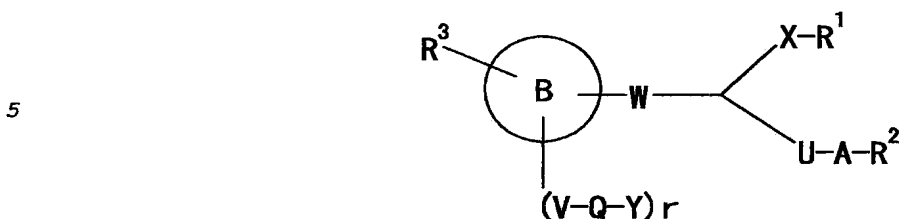
(9) As a platelet aggregation inhibitor, a compound represented by the formula



wherein R<sub>1</sub> is a hydrogen atom, lower alkyl or alkali metal ion; R<sub>1a</sub> is lower alkyl; HET<sub>2</sub> is 4,5-diphenyl-2-thiazolyl, 4,5-diphenyl-1H-imidazol-2-yl, 3,4-diphenyl-1H-pyrazol-1-yl, 4,5-diphenyl-1H-pyrazol-1-yl, 1,5-diphenyl-1H-pyrazol-3-yl and

the like, has been reported (see patent reference 9).

(10) As a therapeutic agent of cardiovascular diseases, a compound represented by the formula



wherein B is C6-10 aryl or a heterocyclic ring containing 1 to 9 carbon atoms and up to 3 heteroatoms; r is 0 or 1; V is void or O and the like; Q is void, O or saturated or unsaturated alkylene and the like; Y is a hydrogen atom and the like; R<sup>3</sup> is  
10 a hydrogen atom, halogen and the like; W is alkylene and the like; U is alkylene and the like; A is void or C6-10 aryl or an aromatic heterocyclic ring containing 1 to 9 carbon atoms and up to 3 heteroatoms; R<sup>2</sup> is CN, tetrazolyl, COOR<sup>26</sup> or CONR<sup>27</sup>R<sup>28</sup> (R<sup>26</sup>, R<sup>27</sup> and R<sup>28</sup> are each a hydrogen atom and the  
15 like); X is alkylene and the like; R<sup>1</sup> is CN, tetrazolyl, COOR<sup>35</sup> or CONR<sup>36</sup>R<sup>37</sup> (R<sup>35</sup>, R<sup>36</sup> and R<sup>37</sup> are each a hydrogen atom and the like) has been reported (see patent reference 10).

【0005】

【non-patent reference 1】

20 Cell, vol. 83, p.803 (1995)

【non-patent reference 2】

The Journal of Biological Chemistry, vol. 270, p.12953 (1995)

【non-patent reference 3】

Journal of Medicinal Chemistry, vol. 39, p.655 (1996)

25 【non-patent reference 4】

Proceedings of the National Academy of Sciences of the United States of America, vol. 94, p.237 (1997)

【non-patent reference 5】

The Journal of Biological Chemistry, vol. 272, p.3406 (1997)

30 【non-patent reference 6】

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States of America, vol. 96, p.6102 (1999)
- 【non-patent reference 10】  
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- 10     【non-patent reference 11】  
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- 【non-patent reference 12】  
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15     (2000)
- 【non-patent reference 13】  
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- 【non-patent reference 14】  
20     The Journal of Biological Chemistry, vol.276, p.10853-10860  
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- 【non-patent reference 15】  
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- 【non-patent reference 16】  
25     Molecular Cell Biology, vol. 20, p.5119-5128 (2000)
- 【non-patent reference 17】  
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- 【non-patent reference 18】  
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- 30     【non-patent reference 19】  
Proceedings of The National Academy of Sciences of The United  
States of America, vol. 98, p.5306-5311 (2001)
- 【non-patent reference 20】  
Cell, vol. 99, p.335-345 (1999)
- 35     【non-patent reference 21】



Proceedings of The National Academy of Sciences of The United States of America, vol. 98, p.2598-2603 (2001)

    【non-patent reference 22】

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5       【non-patent reference 23】

The Journal of Biological Chemistry, vol. 275, p.8126-8132 (2000)

    【non-patent reference 24】

Genes and Development, vol. 15, p.3263-3277 (2001)

10      【non-patent reference 25】

The Journal of Biological Chemistry, vol. 274, p.35881-35888 (1999)

    【patent reference 1】

WO00/64876

15      【patent reference 2】

WO01/38325

    【patent reference 3】

WO01/00603

    【patent reference 4】

20      JP-A-2001-354671

    【patent reference 5】

WO97/31907

    【patent reference 6】

JP-A-4-194845

25      【patent reference 7】

JP-A-4-184435

    【patent reference 8】

WO00/61579

    【patent reference 9】

30      EP-A-442448

    【patent reference 10】

WO01/19778

    【0006】

    【Problems to be Solved by the Invention】

35       There is a demand for development of a 1,2-azole

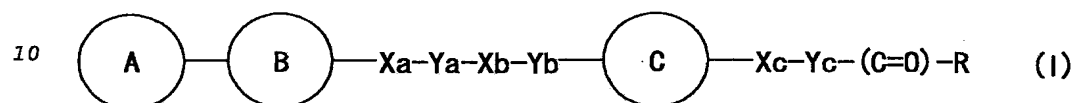
derivative useful as an agent for the prophylaxis or treatment of diabetes mellitus, hyperlipidemia, arteriosclerosis, impaired glucose tolerance etc., and having pharmaceutically excellent properties such as low side effects, etc.

5       **【0007】**

**【Means of Solving the Problems】**

The present invention relates to

1) a compound represented by the formula



wherein

ring A is a ring optionally having 1 to 3 substituents;

ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

15       Xa, Xb and Xc

are the same or different and each is a bond, -O-,  
-S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>-  
or -NR<sup>3</sup>CO- (R<sup>1</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group, R<sup>2</sup> is a hydrogen atom or  
20       a hydroxy-protecting group, R<sup>3</sup> is a hydrogen atom, an  
optionally substituted hydrocarbon group or an amino-  
protecting group);

Ya is a divalent aliphatic hydrocarbon residue having 1  
to 20 carbon atoms;

25       Yb and Yc

are the same or different and each is a bond or a  
divalent aliphatic hydrocarbon residue having 1 to 20  
carbon atoms;

ring C is a monocyclic aromatic ring optionally further  
30       having 1 to 3 substituents;

R represents -OR<sup>4</sup> (R<sup>4</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group) or -NR<sup>5</sup>R<sup>6</sup> (R<sup>5</sup> and R<sup>6</sup> are  
the same or different and each is a hydrogen atom, an

- optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R<sup>5</sup> and R<sup>6</sup> form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring),  
5 provided that,  
(1) when the 1,2-azole ring represented by ring B is pyrazole, ring C is not thiadiazole or oxadiazole;  
(2) when the 1,2-azole ring represented by ring B is isoxazole, ring C is not an optionally substituted  
10 pyridone; and  
(3) when the 1,2-azole ring represented by ring B is pyrazole and Xa and Xb are each a bond, ring C is not a benzene ring,  
or a salt thereof or a prodrug thereof,  
15 2) the compound of the aforementioned 1), wherein the ring represented by ring A is an aromatic ring,  
3) the compound of the aforementioned 2), wherein the aromatic ring is a benzene ring or a pyridine ring,  
4) the compound of the aforementioned 1), wherein the 1,2-  
20 azole ring represented by ring B is pyrazole,  
5) the compound of the aforementioned 1), wherein the substituent that ring B is optionally further having is a hydrocarbon group,  
6) the compound of the aforementioned 1), wherein the  
25 substituent that ring B is optionally further having is an alkoxy group,  
7) the compound of the aforementioned 1), wherein Ya is C<sub>1-6</sub> alkylene or C<sub>2-6</sub> alkenylene,  
8) the compound of the aforementioned 1), wherein Xb is -O-,  
30 -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>- or -NR<sup>3</sup>CO- (R<sup>1</sup> is a hydrogen atom or an optionally substituted hydrocarbon group, R<sup>2</sup> is a hydrogen atom or a hydroxy-protecting group, and R<sup>3</sup> is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group),  
35 9) the compound of the aforementioned 1), wherein the

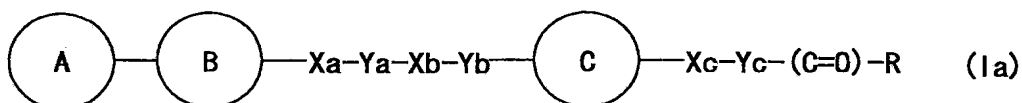
monocyclic aromatic ring represented by ring C is a benzene ring,

10) the compound of the aforementioned 1), wherein the monocyclic aromatic ring represented by ring C is pyrazole,

5 11) the compound of the aforementioned 1), wherein R represents  $-OR^4$  ( $R^4$  is a hydrogen atom or an optionally substituted hydrocarbon group),

12) a pharmaceutical composition comprising the compound of the aforementioned 1) or a salt thereof or a prodrug thereof,

10 13) an agent for the prophylaxis or treatment of diabetes, which comprises a compound represented by the formula



wherein

15 ring A is a ring optionally having 1 to 3 substituents;

ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

Xa, Xb and Xc

are the same or different and each is a bond, -O-,  
20 -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>-  
or -NR<sup>3</sup>CO- ( $R^1$  is a hydrogen atom or an optionally substituted hydrocarbon group,  $R^2$  is a hydrogen atom or a hydroxy-protecting group,  $R^3$  is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

25 Ya is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

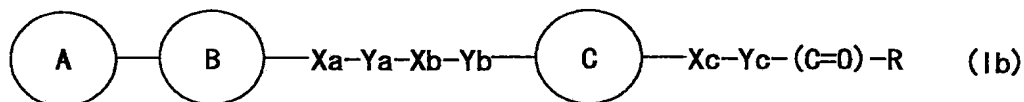
Yb and Yc

are the same or different and each is a bond or a  
30 divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents;

R represents  $-OR^4$  ( $R^4$  is a hydrogen atom or an optionally substituted hydrocarbon group) or  $-NR^5R^6$  ( $R^5$  and  $R^6$  are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or  $R^5$  and  $R^6$  form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring), or a salt thereof or a prodrug thereof,

- 14) an agent for the prophylaxis or treatment of hyperlipidemia, which comprises a compound represented by the formula (Ia) or a salt thereof or a prodrug thereof,
- 15) an agent for the prophylaxis or treatment of arteriosclerosis, which comprises a compound represented by the formula



wherein

ring A is a ring optionally having 1 to 3 substituents;

ring B is a 1,2-azole ring optionally further having 1 to 3 substituents;

$Xa$ ,  $Xb$  and  $Xc$

are the same or different and each is a bond,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$ ,  $-CO-$ ,  $-CS-$ ,  $-CR^1(OR^2)-$ ,  $-NR^3-$ ,  $-CONR^3-$  or  $-NR^3CO-$  ( $R^1$  is a hydrogen atom or an optionally substituted hydrocarbon group,  $R^2$  is a hydrogen atom or a hydroxy-protecting group, and  $R^3$  is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group);

$Ya$  is a divalent aliphatic hydrocarbon residue having 1 to 20 carbon atoms;

$Yb$  and  $Yc$

are the same or different and each is a bond or a divalent aliphatic hydrocarbon residue having 1 to 20

carbon atoms;

ring C is a monocyclic aromatic ring optionally further having 1 to 3 substituents;

R represents  $-OR^4$  ( $R^4$  is a hydrogen atom or an optionally substituted hydrocarbon group) or  $-NR^5R^6$  ( $R^5$  and  $R^6$  are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or  $R^5$  and  $R^6$  form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring), provided that, when the 1,2-azole ring represented by ring B is isoxazole, ring C is not an optionally substituted pyridone,

or a salt thereof or a prodrug thereof.

16) an agent for the prophylaxis or treatment of impaired glucose tolerance, which comprises a compound represented by the formula (Ia) or a salt thereof or a prodrug thereof,

17) a retinoid-related receptor function regulating agent, which comprises a compound represented by the formula (Ia) or a salt thereof or a prodrug thereof,

18) the agent of the aforementioned 17), which is a peroxisome proliferator-activated receptor ligand,

19) the agent of the aforementioned 17), which is a retinoid X receptor ligand,

20) an insulin resistance improving agent, which comprises a compound represented by the formula (Ia) or a salt thereof or a prodrug thereof,

21) a method for the prophylaxis or treatment of diabetes in a mammal, which comprises administering to the mammal a compound represented by the formula (Ia) or a salt thereof or a prodrug thereof,

22) use of a compound represented by the formula (Ia) or a salt thereof or a prodrug thereof, for the production of an agent for the prophylaxis or treatment of diabetes, and the like.

【0008】

The definition of each symbol in the formulas (I), (Ia) and (Ib) is explained in detail in the following.

As the ring represented by ring A, for example, aromatic  
5 rings such as aromatic hydrocarbon, aromatic heterocyclic ring and the like; and non-aromatic rings such as alicyclic hydrocarbon, non-aromatic heterocyclic ring and the like can be mentioned.

As the aromatic hydrocarbon, for example, aromatic  
10 hydrocarbon having 6 to 14 carbon atoms can be mentioned. As preferable examples of the aromatic hydrocarbon, benzene, naphthalene, anthracene, phenanthrene, acenaphthylene, indene and the like can be mentioned. Of these, benzene, naphthalene and the like are preferable.

15 As the aromatic heterocyclic ring, for example, a 5- to 7-membered monocyclic aromatic heterocyclic ring which contains, besides carbon atom, 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom as ring-constituting atom, or condensed aromatic heterocyclic ring can  
20 be mentioned. As the condensed aromatic heterocyclic ring, for example, a ring wherein the above-mentioned 5- to 7-membered monocyclic aromatic heterocyclic ring and a 6-membered ring containing 1 or 2 nitrogen atoms, a benzene ring or a 5-membered ring containing one sulfur atom are condensed, and  
25 the like can be mentioned.

Preferable examples of the aromatic heterocyclic ring include furan, thiophene, pyridine, pyrimidine, pyridazine, pyrazine, pyrrole, imidazole, pyrazole, isoxazole, isothiazole, oxazole, thiazole, oxadiazole, thiadiazole,  
30 triazole, tetrazole, quinoline, quinazolin, quinoxaline, benzofuran, benzothiophene, benzoxazole, benzothiazole, benzimidazole, indole, 1H-indazole, 1H-pyrrolo[2,3-b]pyrazine, 1H-pyrrolopyridine, 1H-imidazopyridine, 1H-imidazopyrazine, triazine, isoquinoline, benzothiadiazole and the like.

35 The aromatic heterocyclic ring is preferably a 5- or 6-

membered aromatic heterocyclic ring, more preferably furan, thiophene, pyridine, pyrimidine, pyrazole, oxazole, thiazole, pyridazine, oxadiazole, thiadiazole and the like.

**[0009]**

5       As the alicyclic hydrocarbon, a saturated or unsaturated alicyclic hydrocarbon having 3 to 12 carbon atoms, for example, cycloalkane, cycloalkene, cycloalkadiene and the like can be mentioned.

Preferable examples of cycloalkane include cycloalkane  
10   having 3 to 10 carbon atoms such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.1]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, bicyclo[4.2.1]nonane,  
15   bicyclo[4.3.1]decane and the like.

Preferable examples of cycloalkene include cycloalkene having 3 to 10 carbon atoms, such as cyclopentene, cyclohexene and the like.

Preferable examples of cycloalkadiene include  
20   cycloalkadiene having 4 to 10 carbon atoms, such as 2,4-cyclopentadiene, 2,4-cyclohexadiene, 2,5-cyclohexadiene and the like.

As the non-aromatic heterocyclic ring, for example, a 5- to 7-membered monocyclic non-aromatic heterocyclic ring which  
25   contains, besides carbon atom, 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom as ring-constituting atom, or condensed non-aromatic heterocyclic ring can be mentioned. As the condensed non-aromatic heterocyclic ring, for example, a ring wherein the above-mentioned 5- to 7-  
30   membered monocyclic non-aromatic heterocyclic ring and a 6-membered ring containing 1 or 2 nitrogen atoms, a benzene ring or a 5-membered ring containing one sulfur atom are condensed, and the like can be mentioned.

Preferable examples of the non-aromatic heterocyclic ring  
35   include pyrrolidine, pyrroline, pyrazolidine, piperidine,



piperazine, morpholine, thiomorpholine, piperazine, hexamethyleneimine, oxazolidine, thiazolidine, imidazolidine, imidazoline, tetrahydrofuran, azepane, tetrahydropyridine and the like.

5       The ring represented by ring A is preferably an aromatic ring such as aromatic hydrocarbon, aromatic heterocyclic ring and the like, more preferably an aromatic hydrocarbon having 6 to 14 carbon atoms or a 5- or 6-membered aromatic heterocyclic ring. Of these, benzene, pyridine and the like are preferable.

10       【0010】

      The ring represented by ring A may have 1 to 3 substituents at substitutable positions. As the substituent, for example, "halogen atom", "nitro group", "cyano group", "optionally substituted aliphatic hydrocarbon group",  
15 "optionally substituted alicyclic hydrocarbon group", "optionally substituted aromatic hydrocarbon group", "optionally substituted aromatic aliphatic hydrocarbon group", "optionally substituted heterocyclic group", "optionally substituted acyl group", "optionally substituted amino group",  
20 "optionally substituted hydroxy group", "optionally substituted thiol group", "optionally esterified or amidated carboxyl group" and the like can be mentioned.

      As the "halogen atom", fluorine, chlorine, bromine and iodine can be mentioned. Of these, fluorine and chlorine are  
25 preferable.

      As the aliphatic hydrocarbon group of the "optionally substituted aliphatic hydrocarbon group", a straight-chain or branched aliphatic hydrocarbon group having 1 to 15 carbon atoms are preferable. As the aliphatic hydrocarbon group, for  
30 example, alkyl group, alkenyl group, alkynyl group and the like can be mentioned.

      Preferable examples of alkyl group include alkyl group having 1 to 10 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl,  
35 isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-

dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl, nonyl, decyl, 1-methylbutyl and the like.

Preferable examples of alkenyl group include alkenyl group having 2 to 10 carbon atoms such as ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl and the like.

Preferable examples of alkynyl group include alkynyl group having 2 to 10 carbon atoms, such as ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl and the like.

#### **【0011】**

As the substituent of the "optionally substituted aliphatic hydrocarbon group", for example, halogen atom (e.g., fluorine, chlorine, bromine, iodine); sulfo group; cyano group; azido group; nitro group; nitroso group; cycloalkyl group having 3 to 10 carbon atoms; aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl); non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidinyl, piperazinyl); amino group which may be mono- or di-substituted by a substituent selected from alkyl group having 1 to 4 carbon atoms and acyl group having 2 to 8 carbon atoms (e.g., alkanoyl group); amidino group; acyl group having 2 to 8 carbon atoms (e.g., alkanoyl group); carbamoyl group which may be mono- or di-substituted by alkyl group having 1 to 4 carbon atoms; sulfamoyl group which may be mono- or di-substituted by alkyl group having 1 to 4 carbon atoms; carboxyl group; alkoxycarbonyl group having 2 to 8 carbon atoms; hydroxy group; alkoxy group having 1 to 6 carbon atoms which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine,

bromine, iodine); aralkyloxy group having 7 to 13 carbon atoms; aryloxy group having 6 to 14 carbon atoms (e.g., phenyloxy, naphthyloxy); thiol group; alkylthio group having 1 to 6 carbon atoms which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine); aralkylthio group having 7 to 13 carbon atoms; arylthio group having 6 to 14 carbon atoms (e.g., phenylthio, naphthylthio) and the like can be mentioned. The number of substituent is, for example, 1 to 3.

10      **[0012]**

As the alicyclic hydrocarbon group of the "an optionally substituted alicyclic hydrocarbon group", saturated or unsaturated alicyclic hydrocarbon group having 3 to 10 carbon atoms is preferable. As the alicyclic hydrocarbon group, for example, cycloalkyl group, cycloalkenyl group, cycloalkadienyl group and the like can be mentioned.

Preferable examples of the cycloalkyl group include cycloalkyl group having 3 to 10 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

Preferable examples of the cycloalkenyl group include cycloalkenyl group having 3 to 10 carbon atoms, such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and the like.

Preferable examples of the cycloalkadienyl group include cycloalkadienyl group having 5 to 10 carbon atoms, such as 2,4-cycloheptadienyl and the like.

**[0013]**

30      As the aromatic hydrocarbon group of the "an optionally substituted aromatic hydrocarbon group", aryl group having 6 to 14 carbon atoms is preferable. As the aryl group, for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthylene and the like can be mentioned. Of these, phenyl, 1-naphthyl, 2-naphthyl and the like are preferable.

As the aromatic aliphatic hydrocarbon group of the "an optionally substituted aromatic aliphatic hydrocarbon group", aromatic aliphatic hydrocarbon group having 7 to 13 carbon atoms is preferable. As the aromatic aliphatic hydrocarbon group, for example, aralkyl group, arylalkenyl group and the like can be mentioned.

Preferable examples of the aralkyl group include aralkyl group having 7 to 13 carbon atoms, such as benzyl, phenethyl, naphthylmethyl, benzhydryl and the like.

10 Preferable examples of the arylalkenyl group include arylalkenyl group having 8 to 13 carbon atoms, such as styryl and the like.

As the heterocyclic group of the "optionally substituted heterocyclic group", for example, a 5- to 7-membered 15 monocyclic heterocyclic group which contains, besides carbon atom, 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom as ring-constituting atom, or condensed heterocyclic group can be mentioned. As the condensed heterocyclic group, for example, a group wherein the above- 20 mentioned 5- to 7-membered monocyclic heterocyclic group is condensed with a 6-membered ring containing 1 or 2 nitrogen atoms, a benzene ring or a 5-membered ring containing one sulfur atom and the like can be mentioned.

Specific examples of the heterocyclic group include 25 aromatic heterocyclic groups such as furyl (2-furyl, 3-furyl), thienyl (2-thienyl, 3-thienyl), pyrrolyl (1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), isoxazolyl (3-isoxazolyl, 4- 30 isoxazolyl, 5-isoxazolyl), isothiazolyl (3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), oxadiazolyl (1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (1,3,4-thiadiazol-2- 35 yl), triazolyl (1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-

triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl),  
tetrazolyl (tetrazol-1-yl, tetrazol-5-yl), pyridyl (2-pyridyl,  
3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-  
pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyridazinyl (3-  
5 pyridazinyl, 4-pyridazinyl), pyrazinyl (2-pyrazinyl), quinolyl  
(2-quinolyl, 3-quinolyl, 4-quinolyl), quinazolyl (2-  
quinazolyl, 4-quinazolyl), quinoxalyl (2-quinoxalyl),  
benzoxazolyl (2-benzoxazolyl), benzothiazolyl (2-  
benzothiazolyl), benzimidazolyl (benzimidazol-1-yl,  
10 benzimidazol-2-yl), indolyl (indol-1-yl, indol-3-yl),  
indazolyl (1H-indazol-3-yl), pyrrolopyrazinyl (1H-pyrrolo[2,3-  
b]pyrazin-2-yl), pyrrolopyridinyl (1H-pyrrolo[2,3-b]pyridin-6-  
yl), imidazopyridinyl (1H-imidazo[4,5-b]pyridin-2-yl, 1H-  
imidazo[4,5-c]pyridin-2-yl), imidazopyrazinyl (1H-imidazo[4,5-  
15 b]pyrazin-2-yl), benzotriazolyl (benzotriazol-1-yl) and the  
like; non-aromatic heterocyclic groups such as pyrrolidinyl  
(1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl),  
imidazolidinyl (2-imidazolidinyl, 4-imidazolidinyl),  
pyrazolidinyl (2-pyrazolidinyl, 3-pyrazolidinyl, 4-  
20 pyrazolidinyl), thiazolidinyl (thiazolidin-3-yl), oxazolidinyl  
(oxazolidin-3-yl), piperidino, morpholino, thiomorpholino,  
piperazinyl (1-piperazinyl), hexamethyleneiminyl  
(hexamethyleneimin-1-yl) and the like.

**[0014]**

25 As the substituent of the aforementioned "optionally  
substituted alicyclic hydrocarbon group", "optionally  
substituted aromatic hydrocarbon group", "optionally  
substituted aromatic aliphatic hydrocarbon group" and  
"optionally substituted heterocyclic group", for example,  
30 halogen atom (e.g., fluorine, chlorine, bromine, iodine);  
sulfo group; cyano group; azido group; nitro group; nitroso  
group; alkyl group having 1 to 6 carbon atoms which may be  
substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine,  
bromine, iodine); alkenyl group having 2 to 6 carbon atoms  
35 which may be substituted by 1 to 3 halogen atoms (e.g.,

fluorine, chlorine, bromine, iodine); cycloalkyl group having 3 to 10 carbon atoms; aryl group having 6 to 14 carbon atoms (e.g., phenyl, naphthyl); aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl); non-aromatic  
5 heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidinyl, piperazinyl); aralkyl group having 7 to 13 carbon atoms; amino group which may be mono- or di- substituted by a substituent selected from alkyl group having 1 to 4 carbon atoms and acyl group having 2  
10 to 8 carbon atoms (e.g., alkanoyl group); amidino group; acyl group having 2 to 8 carbon atoms (e.g., alkanoyl group); carbamoyl group which may be mono- or di-substituted by alkyl group having 1 to 4 carbon atoms; sulfamoyl group which may be mono- or di-substituted by alkyl group having 1 to 4 carbon  
15 atoms; carboxyl group; alkoxy carbonyl group having 2 to 8 carbon atoms; hydroxy group; alkoxy group having 1 to 6 carbon atoms which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine); aralkyloxy group having 7 to 13 carbon atoms; aryloxy group having 6 to 14 carbon  
20 atoms (e.g., phenyloxy, naphthyloxy); thiol group; alkylthio group having 1 to 6 carbon atoms which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine); aralkylthio group having 7 to 13 carbon atoms; arylthio group having 6 to 14 carbon atoms (e.g., phenylthio, naphthylthio) and the like can be mentioned. The number of  
25 substituent is, for example, 1 to 3.

**[0015]**

The acyl group of the "optionally substituted acyl group" is exemplified by an acyl group having 1 to 13 carbon atoms,  
30 which is specifically formyl, a group represented by the formula:  $-\text{COR}^7$ ,  $-\text{SO}_2\text{R}^7$ ,  $-\text{SOR}^7$  or  $-\text{PO}_3\text{R}^7\text{R}^8$  [wherein  $\text{R}^7$  and  $\text{R}^8$  are the same or different and each is hydrocarbon group or heterocyclic group, or  $\text{R}^7$  and  $\text{R}^8$  may form a heterocyclic ring together with the adjacent oxo-substituted phosphorus atom and  
35 two oxygen atoms] and the like.

As the hydrocarbon group represented by R<sup>7</sup> or R<sup>8</sup>, for example, aliphatic hydrocarbon group, alicyclic hydrocarbon group, aromatic hydrocarbon group, aromatic aliphatic hydrocarbon group and the like can be mentioned.

5 As these aliphatic hydrocarbon group, alicyclic hydrocarbon group, aromatic hydrocarbon group and aromatic aliphatic hydrocarbon group, those exemplified as the substituent for ring A can be mentioned.

The hydrocarbon group is preferably alkyl group having 1  
10 to 10 carbon atoms, alkenyl group having 2 to 10 carbon atoms, cycloalkyl group having 3 to 10 carbon atoms, cycloalkenyl group having 3 to 10 carbon atoms, aryl group having 6 to 14 carbon atoms, aralkyl group having 7 to 13 carbon atoms and the like.

15 As the heterocyclic group represented by R<sup>7</sup> or R<sup>8</sup>, those exemplified as the substituent for ring A can be mentioned. The heterocyclic group is preferably thienyl, furyl, pyridyl and the like.

#### 【0016】

20 As the heterocyclic ring formed by R<sup>7</sup> and R<sup>8</sup> together with the adjacent oxo-substituted phosphorus atom and two oxygen atoms, for example, a 4- to 7-membered heterocyclic ring, which contains, besides carbon atom, oxo-substituted phosphorus atom and two oxygen atoms and optionally 1 or 2  
25 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom as ring-constituting atom and the like can be mentioned. Specific examples of the heterocyclic ring include 2-oxide-1,3,2-dioxaphosphinane, 2-oxide-1,3,2-dioxaphospholane and the like.

#### 30 【0017】

Preferable examples of the acyl group include an alkanoyl group having 2 to 10 carbon atoms (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl), an alkenoyl group having 3 to 10 carbon  
35 atoms (e.g., crotonyl), a cycloalkanoyl group having 4 to 10

to 10 carbon atoms, cycloalkenyl group having 3 to 10 carbon atoms, aryl group having 6 to 14 carbon atoms, aralkyl group having 7 to 13 carbon atoms and acyl group having 1 to 13 carbon atoms, those exemplified as the substituent for ring A  
5 can be mentioned.

**【0020】**

Preferable examples of the substituted amino group include mono- or di-C<sub>1-10</sub> alkylamino (e.g., methylamino, dimethylamino, ethylamino, diethylamino, ethylmethylamino,  
10 propylamino, dibutylamino), mono- or di-C<sub>2-10</sub> alkenylamino (e.g., diallylamino), mono- or di-C<sub>3-10</sub> cycloalkylamino (e.g., cyclohexylamino), mono- or di-C<sub>2-10</sub> alkanoylamino (e.g., acetylamino, propionylamino, butyrylamino, isobutyrylamino),  
15 benzoylamino), arylamino having 6 to 14 carbon atoms (e.g., phenylamino), N-C<sub>1-10</sub> alkyl-N-C<sub>6-14</sub> arylamino (e.g., N-methyl-N-phenylamino), C<sub>1-10</sub> alkylsulfonylamino (e.g., methylsulfonylamino) and the like.

**【0021】**

20 As the "optionally substituted hydroxy group", for example, a hydroxy group which may be substituted by an "alkyl group having 1 to 10 carbon atoms", "alkenyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms",  
25 "aryl group having 6 to 14 carbon atoms", "aralkyl group having 7 to 13 carbon atoms" or "acyl group having 1 to 13 carbon atoms", each of which may be substituted, can be mentioned.

As these "alkyl group having 1 to 10 carbon atoms",  
30 "alkenyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms", "aralkyl group having 7 to 13 carbon atoms" and "acyl group having 1 to 13 carbon atoms", those exemplified as the  
35 substituent for ring A can be mentioned.



carbon atoms (e.g., cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl), a cycloalkenoyl group having 4 to 10 carbon atoms (e.g., 2-cyclohexenecarbonyl), an arylcarbonyl group having 7 to 13 carbon atoms (e.g., benzoyl), an aromatic heterocyclic carbonyl group (e.g., nicotinoyl, isonicotinoyl), alkylsulfinyl group having 1 to 10 carbon atoms (e.g., methylsulfinyl, ethylsulfinyl), an alkylsulfonyl group having 1 to 10 carbon atoms (e.g., methylsulfonyl, ethylsulfonyl), a (mono- or di-alkyl having 1 to 10 carbon atoms)phosphono group optionally forming a ring (e.g., dimethylphosphono, diethylphosphono, diisopropylphosphono, dibutylphosphono, 2-oxide-1,3,2-dioxaphosphinanyl) and the like.

**[0018]**

The acyl group may have 1 to 3 substituents at substitutable positions, and as such substituent, for example, a C<sub>1-6</sub> alkyl group (e.g., methyl, ethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, iodine), a C<sub>1-6</sub> alkoxy group (e.g., methoxy, ethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro group, a hydroxy group, an amino group and the like can be mentioned.

**[0019]**

As the "optionally substituted amino group", an amino group which may be mono- or di-substituted by a substituent selected from, for example, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, a cycloalkyl group having 3 to 10 carbon atoms, a cycloalkenyl group having 3 to 10 carbon atoms, an aryl group having 6 to 14 carbon atoms, an aralkyl group having 7 to 13 carbon atoms and an acyl group having 1 to 13 carbon atoms can be mentioned.

As these alkyl group having 1 to 10 carbon atoms, alkenyl group having 2 to 10 carbon atoms, cycloalkyl group having 3

These "alkyl group having 1 to 10 carbon atoms", "alkenyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms", "aralkyl group having 7 to 13 carbon atoms" and "acyl group having 1 to 13 carbon atoms" may have 1 to 3 substituents at substitutable positions. As such substituents, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C<sub>1-6</sub> alkoxy group (e.g., methoxy, ethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine), a hydroxy group, a nitro group, an amino group and the like can be mentioned.

**[0022]**

As the substituted hydroxy group, for example, an alkoxy group, an alkenyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, an aryloxy group, an aralkyloxy group, an acyloxy group and the like, each of which may be substituted, can be mentioned.

Preferable examples of the alkoxy group include an alkoxy group having 1 to 10 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy and the like.

Preferable examples of the alkenyloxy group include an alkenyloxy group having 2 to 10 carbon atoms, such as allyloxy, crotyloxy, 2-pentyloxy, 3-hexenyloxy and the like.

Preferable examples of the cycloalkyloxy group include a cycloalkyloxy group having 3 to 10 carbon atoms, such as cyclobutoxy, cyclopentyloxy, cyclohexyloxy and the like.

Preferable examples of the cycloalkenyloxy group include a cycloalkenyloxy group having 3 to 10 carbon atoms, such as 2-cyclopentyloxy, 2-cyclohexenyloxy and the like.

Preferable examples of the aryloxy group include an aryloxy group having 6 to 14 carbon atoms, such as phenoxy, naphthyloxy and the like.

Preferable examples of the aralkyloxy group include an aralkyloxy group having 7 to 13 carbon atoms, such as benzyloxy, phenethyloxy, naphthylmethyloxy and the like.

Preferable examples of the acyloxy group include an  
5 acyloxy group having 2 to 13 carbon atoms, such as an alkanoyloxy having 2 to 4 carbon atoms (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy) and the like.

**[0023]**

The above-mentioned alkoxy group, alkenyloxy group,  
10 cycloalkyloxy group, cycloalkenyloxy group, aryloxy group, aralkyloxy group and acyloxy group may have 1 to 3 substituents at substitutable positions. Examples of such substituent include a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C<sub>1-6</sub> alkoxy group (e.g., methoxy, ethoxy)  
15 which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine), a hydroxy group, a nitro group, an amino group and the like.

**[0024]**

As the optionally substituted thiol group, for example, a  
20 thiol group which may be substituted by an "alkyl group having 1 to 10 carbon atoms", "alkenyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms", "aralkyl group having 7 to 13  
25 carbon atoms" or "acyl group having 1 to 13 carbon atoms", each of which may be substituted, can be mentioned.

As used herein, as the "alkyl group having 1 to 10 carbon atoms", "alkenyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl  
30 group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms", "aralkyl group having 7 to 13 carbon atoms" and "acyl group having 1 to 13 carbon atoms", those exemplified as the substituent for ring A can be mentioned.

These "alkyl group having 1 to 10 carbon atoms", "alkenyl  
35 group having 2 to 10 carbon atoms", "cycloalkyl group having 3

to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms", "aralkyl group having 7 to 13 carbon atoms" and "acyl group having 1 to 13 carbon atoms" may have 1 to 3 substituent(s) at  
5 substitutable positions. As such substituents, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C<sub>1-6</sub> alkoxy group (e.g., methoxy, ethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine), a hydroxy group, a nitro group, an amino group and  
10 the like can be mentioned.

**[0025]**

As the substituted thiol group, for example, an alkylthio group, an alkenylthio group, a cycloalkylthio group, a cycloalkenylthio group, an arylthio group, an aralkylthio  
15 group, an acylthio group and the like, each of which may be substituted, can be mentioned.

Preferable examples of the alkylthio group include an alkylthio group having 1 to 10 carbon atoms, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio,  
20 isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio and the like.

Preferable examples of the alkenylthio group include an alkenylthio group having 2 to 10 carbon atoms, such as  
25 allylthio, crotylthio, 2-pentenylthio, 3-hexenylthio and the like.

Preferable examples of the cycloalkylthio group include a cycloalkylthio group having 3 to 10 carbon atoms, such as cyclobutylthio, cyclopentylthio, cyclohexylthio and the like.

30 Preferable examples of the cycloalkenylthio group include a cycloalkenylthio group having 3 to 10 carbon atoms, such as 2-cyclopentenylthio, 2-cyclohexenylthio and the like.

Preferable examples of the arylthio group include an arylthio group having 6 to 14 carbon atoms, such as  
35 phenylthio, naphthylthio and the like.

Preferable examples of the aralkylthio group include an aralkylthio group having 7 to 13 carbon atoms, such as benzylthio, phenethylthio, naphthylmethylthio and the like.

Preferable examples of the acylthio group include an  
5 acylthio group having 2 to 13 carbon atoms, such as alkanoylthio group having 2 to 4 carbon atoms (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio) and the like.

**[0026]**

10 The above-mentioned alkylthio group, alkenylthio group, cycloalkylthio group, cycloalkenylthio group, arylthio group, aralkylthio group and acylthio group may have 1 to 3 substituent(s) at substitutable positions. As such substituents, for example, a halogen atom (e.g., fluorine,  
15 chlorine, bromine, iodine), a C<sub>1-6</sub> alkoxy group (e.g., methoxy, ethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine), a hydroxy group, a nitro group, an amino group and the like can be mentioned.

**[0027]**

20 As the esterified carboxyl group of the optionally esterified carboxyl group, for example, an alkoxycarbonyl group having 2 to 5 carbon atoms (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl), an aralkyloxycarbonyl group having 8 to 14 carbon atoms (e.g.,  
25 benzyloxycarbonyl), an aryloxycarbonyl group having 7 to 15 carbon atoms (e.g., phenoxycarbonyl) and the like can be mentioned.

**[0028]**

As the amidated carboxyl group of the optionally amidated  
30 carboxyl group, a group of the formula: -CON(R<sup>9</sup>)(R<sup>10</sup>) [wherein R<sup>9</sup> and R<sup>10</sup> are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R<sup>9</sup> and R<sup>10</sup> may  
35 form, together with the adjacent nitrogen atom, an optionally substituted nitrogen-containing heterocyclic ring] can be

mentioned.

As used herein, the hydrocarbon group of the "optionally substituted hydrocarbon group" represented by  $R^9$  and  $R^{10}$  is exemplified by the hydrocarbon groups exemplified for the  
5   aforementioned  $R^7$ . The hydrocarbon group is preferably an alkyl group having 1 to 10 carbon atoms (preferably methyl, ethyl, propyl, isopropyl, butyl, tert-butyl), an alkynyl group having 2 to 10 carbon atoms (preferably 2-propynyl), a  
10   cycloalkyl group having 3 to 10 carbon atoms (preferably cyclopropyl, cyclohexyl), an aryl group having 6 to 14 carbon atoms (preferably phenyl), an aralkyl group having 7 to 13 carbon atoms (preferably benzyl, phenethyl, naphthylmethyl) and the like.

As the substituent of the "optionally substituted  
15   hydrocarbon group" represented by  $R^9$  and  $R^{10}$ , for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine); a sulfo group; a cyano group; an azido group; a nitro group; a nitroso group; an aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl); a non-aromatic  
20   heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidinyl, piperazinyl); an amino group which may be mono- or di-substituted by a substituent selected from alkyl group having 1 to 4 carbon atoms and acyl group having 2 to 8 carbon atoms (e.g.,  
25   alkanoyl group); an amidino group; an acyl group having 2 to 8 carbon atoms (e.g., alkanoyl group); a carbamoyl group which may be mono- or di-substituted by alkyl group having 1 to 4 carbon atoms; a sulfamoyl group which may be mono- or di-substituted by alkyl group having 1 to 4 carbon atoms; a  
30   carboxyl group; an alkoxycarbonyl group having 2 to 8 carbon atoms; a hydroxy group; an alkoxy group having 1 to 6 carbon atoms which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine); an alkenyloxy group having 2 to 5 carbon atoms which may be substituted by 1 to 3  
35   halogen atoms (e.g., fluorine, chlorine, bromine, iodine); a

cycloalkyloxy group having 3 to 7 carbon atoms; an aralkyloxy group having 7 to 13 carbon atoms; an aryloxy group having 6 to 14 carbon atoms (e.g., phenyloxy, naphthyloxy); a thiol group; an alkylthio group having 1 to 6 carbon atoms which may  
5 be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine); an aralkylthio group having 7 to 13 carbon atoms; an arylthio group having 6 to 14 carbon atoms (e.g., phenylthio, naphthylthio) and the like can be mentioned. The number of the substituent is, for example, 1 to  
10 3.

**[0029]**

As the heterocyclic group of the "optionally substituted heterocyclic group" represented by  $R^9$  and  $R^{10}$ , the heterocyclic group exemplified for the aforementioned  $R^7$  can be mentioned.

15 As the substituent for the heterocyclic group, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine); a sulfo group; a cyano group; an azido group; a nitro group; a nitroso group; an alkyl group having 1 to 6 carbon atoms which may be substituted by 1 to 3 halogen atoms (e.g.,  
20 fluorine, chlorine, bromine, iodine); an alkenyl group having 2 to 6 carbon atoms which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine); a cycloalkyl group having 3 to 10 carbon atoms; an aryl group having 6 to 14 carbon atoms (e.g., phenyl, naphthyl); an  
25 aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl); a non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidinyl, piperazinyl); an aralkyl group having 7 to 13 carbon atoms; an amino group which may be mono- or di-  
30 substituted by a substituent selected from alkyl group having 1 to 4 carbon atoms and acyl group having 2 to 8 carbon atoms (e.g., alkanoyl group); an amidino group; an acyl group having 2 to 8 carbon atoms (e.g., alkanoyl group); a carbamoyl group which may be mono- or di-substituted by alkyl group having 1  
35 to 4 carbon atoms; a sulfamoyl group which may be mono- or di-

substituted by alkyl group having 1 to 4 carbon atoms; a carboxyl group; an alkoxy carbonyl group having 2 to 8 carbon atoms; a hydroxy group; an alkoxy group having 1 to 6 carbon atoms which may be substituted by 1 to 3 halogen atoms (e.g.,  
5 fluorine, chlorine, bromine, iodine); an alkenyloxy group having 2 to 5 carbon atoms which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine); a cycloalkyloxy group having 3 to 7 carbon atoms; an aralkyloxy group having 7 to 13 carbon atoms; an aryloxy group having 6  
10 to 14 carbon atoms (e.g., phenyloxy, naphthyloxy); a thiol group; an alkylthio group having 1 to 6 carbon atoms which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine); an aralkylthio group having 7 to 13 carbon atoms; an arylthio group having 6 to 14 carbon atoms  
15 (e.g., phenylthio, naphthylthio) and the like can be mentioned. The number of substituent is, for example, 1 to 3.

**[0030]**

As the nitrogen-containing heterocyclic ring formed by R<sup>9</sup> and R<sup>10</sup> together with the adjacent nitrogen atom, for example,  
20 a 5- to 8-membered nitrogen-containing heterocyclic ring which contains, besides carbon atom, at least one nitrogen atom and optionally 1 or 2 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom can be mentioned. Preferable examples of the nitrogen-containing heterocyclic ring include  
25 pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine, azepane and the like.

The nitrogen-containing heterocyclic ring may have 1 or 2 substituents at substitutable positions. As such substituent, a C<sub>1-6</sub> alkyl group (e.g., methyl, ethyl) which may be  
30 substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine); a C<sub>7-14</sub> aralkyl group (e.g., benzyl, diphenylmethyl); a C<sub>6-14</sub> aryl group (e.g., phenyl) which may be substituted by a substituent selected from a C<sub>1-6</sub> alkyl group (e.g., methyl, trifluoromethyl) which may be substituted by 1  
35 to 3 halogen atoms (e.g., fluorine, chlorine, bromine,



iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C<sub>1-6</sub> alkoxy group (e.g., methoxy, ethoxy) or C<sub>2-10</sub> alkanoyl group (e.g., acetyl); a cyano group; a hydroxy group; a C<sub>2-7</sub> alkoxy carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl) and the like can be mentioned.

**[0031]**

The substituent for ring A is preferably a halogen atom, an optionally substituted aliphatic hydrocarbon group, an optionally substituted aromatic hydrocarbon group, an optionally substituted hydroxy group, a optionally substituted thiol group, a nitro group, a cyano group or an optionally substituted amino group, more preferably

- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);
- 4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 6) a nitro group;
- 7) a cyano group; or
- 8) an amino group (e.g., amino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, methylsulfonylamino) which may be substituted by C<sub>2-10</sub> alkanoyl group or C<sub>1-10</sub> alkylsulfonyl group. The number of substituent is preferably 1 or 2.

**[0032]**

The ring A is preferably an aromatic ring (preferably aromatic hydrocarbon, aromatic heterocyclic ring) which may have 1 to 3 substituents selected from a halogen atom, an

optionally substituted aliphatic hydrocarbon group, an optionally substituted aromatic hydrocarbon group, an optionally substituted hydroxy group, an optionally substituted thiol group, a nitro group, a cyano group, an optionally substituted amino group and the like, more preferably an aromatic hydrocarbon having 6 to 14 carbon atoms (preferably benzene) or a 5- or 6-membered aromatic heterocyclic ring (preferably pyridine, pyrimidine, pyridazine, oxadiazole, thiadiazole; more preferably pyridine, pyridazine), each of which may have 1 to 3 substituents selected from

- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);
- 4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 6) a nitro group;
- 7) a cyano group;
- 8) an amino group (e.g., amino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, methylsulfonylamino) which may be substituted by C<sub>2-10</sub> alkanoyl group or C<sub>1-10</sub> alkylsulfonyl group; and the like.

**[0033]**

As the 1,2-azole ring represented by ring B, for example, pyrazole, isoxazole, isothiazole and the like can be mentioned. Of these, pyrazole is preferable.

The 1,2-azole ring represented by ring B may have 1 to 3

substituents at substitutable positions. As such substituent, "a halogen atom", "a nitro group", "a cyano group", "an optionally substituted aliphatic hydrocarbon group", "an optionally substituted alicyclic hydrocarbon group", "an optionally substituted aromatic hydrocarbon group", "an optionally substituted heterocyclic group", "an optionally substituted acyl group", "an optionally substituted amino group", "an optionally substituted hydroxy group", "an optionally substituted thiol group", "an optionally esterified or amidated carboxyl group" and the like exemplified as the substituent for ring A can be mentioned.

The substituent for ring B is preferably "an optionally substituted aliphatic hydrocarbon group", "an optionally substituted alicyclic hydrocarbon group", "an optionally substituted aromatic hydrocarbon group", "an optionally substituted hydroxy group" and the like, more preferably a hydrocarbon group such as aliphatic hydrocarbon group, alicyclic hydrocarbon group, aromatic hydrocarbon group and the like; an alkoxy group; an aralkyloxy group and the like.

Specific examples of the substituent include an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl, 1-ethylpropyl, 1-methylbutyl), an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy), an aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy), a hydroxy group, an aryl group having 6 to 14 carbon atoms (e.g., phenyl), a cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclohexyl) and the like.

#### 【0034】

The ring B is preferably a 1,2-azole ring (preferably pyrazole, isoxazole, isothiazole) which may have 1 to 3 substituents selected from an optionally substituted aliphatic hydrocarbon group, an optionally substituted alicyclic hydrocarbon group, an optionally substituted aromatic hydrocarbon group, an optionally substituted hydroxy group and the like, more preferably pyrazole or isoxazole (preferably

pyrazole) optionally having 1 to 3 substituents selected from an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl, 1-ethylpropyl, 1-methylbutyl), an alkoxy group having 1 to 6 carbon atoms  
5 (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy), an aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy), a hydroxy group, an aryl group having 6 to 14 carbon atoms (e.g., phenyl), a cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclohexyl) and the like.

10 **[0035]**

Xa, Xb and Xc are the same or different and each is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-, -CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-,  
-CONR<sup>3</sup>- or -NR<sup>3</sup>CO- (R<sup>1</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group, R<sup>2</sup> is a hydrogen atom or a  
15 hydroxy-protecting group, R<sup>3</sup> is a hydrogen atom, an optionally substituted hydrocarbon group or an amino-protecting group).

As the "optionally substituted hydrocarbon group" represented by R<sup>1</sup> or R<sup>3</sup>, those exemplified as the  
aforementioned R<sup>9</sup> can be mentioned.

20 The "optionally substituted hydrocarbon group" is preferably an optionally substituted alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl). The alkyl group may have 1 to 3 substituents at substitutable positions, and as such  
25 substituent, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), an alkoxy group having 1 to 4 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy), a hydroxy group, a nitro group, an amino group, an acyl group having 1 to 4  
30 carbon atoms (e.g., alkanoyl group having 1 to 4 carbon atoms such as formyl, acetyl, propionyl etc.) and the like can be mentioned.

**[0036]**

As the hydroxy-protecting group represented by R<sup>2</sup>, for  
35 example, a C<sub>1-6</sub> alkyl group (e.g., methyl, ethyl, propyl,

isopropyl, butyl, tert-butyl), a phenyl group, a trityl group, a C<sub>7-10</sub> aralkyl group (e.g., benzyl), a formyl group, a C<sub>1-6</sub> alkyl-carbonyl group (e.g., acetyl, propionyl), a benzoyl group, a C<sub>7-10</sub> aralkyl-carbonyl group (e.g., benzylcarbonyl), a  
5 2-tetrahydropyranyl group, a 2-tetrahydrofuranyl group, a silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), a C<sub>2-6</sub> alkenyl group (e.g., 1-allyl) and the like can be mentioned. These groups may be substituted by 1 to  
10 3 substituents selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C<sub>1-6</sub> alkyl group (e.g., methyl, ethyl, propyl), a C<sub>1-6</sub> alkoxy group (e.g., methoxy, ethoxy, propoxy), a nitro group and the like.

As the amino-protecting group represented by R<sup>3</sup>, for  
15 example, a formyl group, a C<sub>1-6</sub> alkyl-carbonyl group (e.g., acetyl, propionyl), a C<sub>1-6</sub> alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl), a benzoyl group, a C<sub>7-10</sub> aralkyl-carbonyl group (e.g., benzylcarbonyl), a C<sub>7-14</sub> aralkyloxy-carbonyl group (e.g.,  
20 benzyloxycarbonyl, a 9-fluorenylmethoxycarbonyl), a trityl group, a phthaloyl group, an N,N-dimethylaminomethylene group, a silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), a C<sub>2-6</sub> alkenyl group (e.g., 1-allyl) and the  
25 like can be mentioned. These groups may be substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C<sub>1-6</sub> alkoxy group (e.g., methoxy, ethoxy, propoxy), a nitro group and the like.

R<sup>1</sup> and R<sup>3</sup> are preferably a hydrogen atom or an alkyl  
30 group having 1 to 6 carbon atoms, R<sup>2</sup> is preferably a hydrogen atom.

#### 【0037】

Xa is preferably a bond, -O-, -NR<sup>3</sup>- or -CONR<sup>3</sup>- (R<sup>3</sup> is preferably a hydrogen atom or an alkyl group having 1 to 6  
35 carbon atoms), more preferably a bond or -O-, particularly

preferably a bond.

Xb is preferably -O-, -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CS-,  
-CR<sup>1</sup>(OR<sup>2</sup>)-, -NR<sup>3</sup>-, -CONR<sup>3</sup>- or -NR<sup>3</sup>CO- (R<sup>1</sup> and R<sup>3</sup> are preferably a  
hydrogen atom or an alkyl group having 1 to 6 carbon atoms;  
5 and R<sup>2</sup> is preferably a hydrogen atom), more preferably a bond  
or  
-O-, particularly preferably -O-.

Xc is preferably a bond or -O-.

**[0038]**

10 As the "divalent aliphatic hydrocarbon residue having 1  
to 20 carbon atoms" represented by Ya, Yb and Yc, for example,  
an alkylene having 1 to 20 carbon atoms, an alkenylene having  
2 to 20 carbon atoms, an alkynylene having 2 to 20 carbon  
atoms and the like can be mentioned.

15 The "divalent aliphatic hydrocarbon residue having 1 to  
20 carbon atoms" is preferably a divalent aliphatic  
hydrocarbon group having 1 to 6 carbon atoms, more preferably  
(1) a C<sub>1-6</sub> alkylene (e.g., -CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>-, -(CH<sub>2</sub>)<sub>4</sub>-,  
-(CH<sub>2</sub>)<sub>5</sub>-, -(CH<sub>2</sub>)<sub>6</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -(CH(CH<sub>3</sub>))<sub>2</sub>-,  
20 -(CH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>C(CH<sub>3</sub>)<sub>2</sub>- and the like);  
(2) a C<sub>2-6</sub> alkenylene (e.g., -CH=CH-, -CH<sub>2</sub>-CH=CH-, -C(CH<sub>3</sub>)<sub>2</sub>-  
CH=CH-, -CH<sub>2</sub>-CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-CH=CH-, -CH=CH-CH=CH-, -CH=CH-  
CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>- and the like); or  
(3) a C<sub>2-6</sub> alkynylene (e.g., -C≡C-, -CH<sub>2</sub>-C≡C-, -CH<sub>2</sub>-C≡C-CH<sub>2</sub>-CH<sub>2</sub>-  
25 and the like) and the like.

Of these, a C<sub>1-6</sub> alkylene and a C<sub>2-6</sub> alkenylene are  
preferable.

Ya is preferably a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene.  
When Xa and Xb are bonds, Ya is preferably a C<sub>3-6</sub> alkylene or a  
30 C<sub>3-6</sub> alkenylene.

Yb is preferably a bond, a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub>  
alkenylene, more preferably a bond.

Yc is preferably a bond, a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub>  
alkenylene, more preferably a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene.

35 **[0039]**

As the monocyclic aromatic ring represented by ring C, monocyclic ring from among the aromatic hydrocarbon and aromatic heterocyclic ring exemplified for the aforementioned ring A can be mentioned.

5       The monocyclic aromatic ring is preferably a benzene or a 5- or 6-membered monocyclic aromatic heterocyclic ring, more preferably benzene, pyrazole and the like.

      The monocyclic aromatic ring represented by ring C may have 1 to 3 substituents at substitutable positions. As the  
10   substituent, "a halogen atom", "a nitro group", "a cyano group", "an optionally substituted aliphatic hydrocarbon group", "an optionally substituted alicyclic hydrocarbon group", "an optionally substituted aromatic hydrocarbon group", "an optionally substituted heterocyclic group", "an  
15   optionally substituted acyl group", "an optionally substituted amino group", "an optionally substituted hydroxy group", "an optionally substituted thiol group", "an optionally esterified or amidated carboxyl group" and the like exemplified as substituent for ring A can be mentioned.

20       The substituent for ring C is preferably a halogen atom, an optionally substituted aliphatic hydrocarbon group, an optionally substituted aromatic hydrocarbon group, an optionally substituted hydroxy group, an optionally substituted thiol group, a cyano group, an optionally  
25   substituted alicyclic hydrocarbon group and the like, more preferably

- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be  
30   substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 35   4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy,

ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

- 5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 6) a hydroxy group;
- 7) an aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy);
- 8) a cyano group;
- 9) a cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclohexyl); and the like.

The ring C is preferably a benzene or a 5- or 6-membered monocyclic aromatic heterocyclic ring (preferably pyrazole), which may have 1 to 3 substituents selected from a halogen atom, an optionally substituted aliphatic hydrocarbon group, an optionally substituted aromatic hydrocarbon group, an optionally substituted hydroxy group, an optionally substituted thiol group, a cyano group, an optionally substituted alicyclic hydrocarbon group and the like; more preferably a benzene or a 5- or 6-membered monocyclic aromatic heterocyclic ring (preferably pyrazole), which may have 1 to 3 substituents selected from

- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);



- 5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 6) a hydroxy group;
- 5 7) an aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy);
- 8) a cyano group;
- 9) a cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclohexyl); and the like.

10 **[0040]**

R represents  $-OR^4$  ( $R^4$  is a hydrogen atom or an optionally substituted hydrocarbon group) or  $-NR^5R^6$  ( $R^5$  and  $R^6$  are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted  
15 heterocyclic group, or  $R^5$  and  $R^6$  form, together with the adjacent nitrogen atom, an optionally substituted heterocyclic ring).

As the "optionally substituted hydrocarbon group" represented by  $R^4$ ,  $R^5$  and  $R^6$ , those exemplified as the  
20 aforementioned  $R^9$  can be mentioned.

The "optionally substituted hydrocarbon group" is preferably an optionally substituted alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl).

25 As the "optionally substituted heterocyclic group" represented by  $R^5$  and  $R^6$ , those exemplified as the aforementioned  $R^9$  can be mentioned.

As the "optionally substituted heterocyclic ring" formed by  $R^5$  and  $R^6$  together with the adjacent nitrogen atom, the  
30 aforementioned optionally substituted nitrogen-containing heterocyclic ring" formed by  $R^9$  and  $R^{10}$  together with the adjacent nitrogen atom can be mentioned.

R is preferably  $-OR^4$  ( $R^4$  is a hydrogen atom or an optionally substituted hydrocarbon group). As used herein,  $R^4$   
35 is preferably a hydrogen atom or an alkyl group having 1 to 6

carbon atoms (preferably methyl, ethyl and the like), more preferably a hydrogen atom.

**【0041】**

In the formula (I),

- 5 (1) when the 1,2-azole ring represented by ring B is pyrazole, ring C is not thiadiazole or oxadiazole;  
(2) when the 1,2-azole ring represented by ring B is isoxazole, ring C is not an optionally substituted pyridone;  
(3) when the 1,2-azole ring represented by ring B is pyrazole  
10 and Xa and Xb are bonds, ring C is not a benzene ring.

In the formula (Ib),

when the 1,2-azole ring represented by ring B is isoxazole, ring C is not an optionally substituted pyridone.

**【0042】**

- 15 Preferable examples of the compound represented by the formula (I) include the following compounds.

[compound A]

A compound wherein

- ring A is an aromatic hydrocarbon having 6 to 14 carbon atoms  
20 (preferably benzene) or a 5- or 6-membered aromatic heterocyclic ring (preferably pyridine), each of which may have 1 to 3 substituents selected from  
1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);  
2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl,  
25 ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);  
3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);  
4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy,  
30 ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);  
5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms  
35 (e.g., fluorine, chlorine, bromine, iodine) and the like,

ring B is pyrazole or isoxazole (preferably pyrazole)  
optionally having 1 to 3 substituents selected from an alkyl  
group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl,  
isopropyl), an alkoxy group having 1 to 6 carbon atoms (e.g.,  
5 methoxy, ethoxy, propoxy, isopropoxy, butoxy), an aralkyloxy  
group having 7 to 13 carbon atoms (e.g., benzyloxy) and the  
like;  
Xa is a bond or -O-;  
Xb is a bond or -O-;  
10 Xc is a bond or -O-;  
Ya is a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene;  
Yb is a bond;  
Yc is a bond, a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene;  
ring C is benzene optionally having 1 to 3 substituents  
15 selected from  
1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);  
2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl,  
ethyl, propyl, isopropyl, trifluoromethyl) which may be  
substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine,  
20 bromine, iodine);  
3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);  
4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy,  
ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which  
may be substituted by 1 to 3 halogen atoms (e.g., fluorine,  
25 chlorine, bromine, iodine);  
5) an alkylthio group having 1 to 6 carbon atoms (e.g.,  
methylthio) which may be substituted by 1 to 3 halogen atoms  
(e.g., fluorine, chlorine, bromine, iodine) and the like; and  
R is -OR<sup>4</sup> (R<sup>4</sup> is preferably a hydrogen atom or an alkyl group  
30 having 1 to 6 carbon atoms).

**[0043]**

[compound B]

A compound wherein  
ring A is an aromatic hydrocarbon having 6 to 14 carbon atoms  
35 (preferably benzene) or a 5- or 6-membered aromatic

heterocyclic ring (preferably pyridine), each of which may have 1 to 3 substituents selected from

- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
  - 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
  - 3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);
  - 4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
  - 5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and the like,
- ring B is pyrazole or isoxazole (preferably pyrazole), each of which may have 1 to 3 substituents selected from an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl), an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy), an aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy); and the like;

Xa is a bond or -O-;

Xb is a bond or -O-;

Xc is a bond or -O-;

Ya is a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene;

Yb is a bond;

Yc is a bond, a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene;

ring C is a 5- or 6-membered monocyclic aromatic heterocyclic ring (preferably pyrazole), which may have 1 to 3 substituents selected from

- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine,

bromine, iodine);

3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);

4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which  
5 may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine); and the like; and

10 R is  $-OR^4$  ( $R^4$  is preferably a hydrogen atom or an alkyl group having 1 to 6 carbon atoms).

【0044】

[compound C]

A compound wherein

15 ring A is an aromatic hydrocarbon having 6 to 14 carbon atoms (preferably benzene), a 5- or 6-membered aromatic heterocyclic ring (preferably pyridine) or an alicyclic hydrocarbon having 3 to 12 carbon atoms (preferably cyclopentane), each of which may have 1 to 3 substituents selected from

20 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);  
2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

25 3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);  
4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

30 5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and the like;  
ring B is a pyrazole or isoxazole (preferably pyrazole), each of which may have 1 to 3 substituents selected from an alkyl  
35 group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl,

isopropyl), an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy), an aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy), a hydroxy group, an aryl group having 6 to 14 carbon atoms (e.g.,  
5 phenyl) and the like;  
Xa is a bond or -O-;  
Xb is a bond or -O-;  
Xc is a bond or -O-;  
Ya is a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene;  
10 Yb is a bond;  
Yc is a bond, a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene;  
ring C is a benzene optionally having 1 to 3 substituents selected from  
1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);  
15 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);  
3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl)  
20 which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);  
4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine,  
25 chlorine, bromine, iodine);  
5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);  
6) a hydroxy group;  
30 7) an aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy); and the like; and  
R is -OR<sup>4</sup> (R<sup>4</sup> is preferably a hydrogen atom or an alkyl group having 1 to 6 carbon atoms).

【0045】

35 [compound D]

A compound wherein ring A is an aromatic hydrocarbon having 6 to 14 carbon atoms (preferably benzene), a 5- or 6-membered aromatic heterocyclic ring (preferably pyridine) or an alicyclic hydrocarbon having 3 to 12 carbon atoms

5 (preferably cyclopentane), each of which may have 1 to 3 substituents selected from

- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be
- 10 substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);
- 4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which
- 15 may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and the like;
- 20 ring B is a pyrazole or isoxazole (preferably pyrazole) optionally having an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl), an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy), an aralkyloxy group having 7 to 13 carbon
- 25 atoms (e.g., benzyloxy), a hydroxy group, an aryl group having 6 to 14 carbon atoms (e.g., phenyl) and the like;

Xa is a bond or -O-;

Xb is a bond or -O-;

Xc is a bond or -O-;

30 Ya is a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene;

Yb is a bond;

Yc is a bond, a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene;

ring C is a 5- or 6-membered monocyclic aromatic heterocyclic ring (preferably pyrazole) optionally having 1 to 3

35 substituents selected from

- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
  - 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
  - 3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
  - 4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
  - 5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
  - 6) a hydroxy group;
  - 7) an aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy); and the like; and
- R is  $-OR^4$  ( $R^4$  is preferably a hydrogen atom or an alkyl group having 1 to 6 carbon atoms).

【0046】

[compound E]

A compound wherein ring A is an aromatic hydrocarbon having 6 to 14 carbon atoms (preferably benzene), a 5- or 6-membered aromatic heterocyclic ring (preferably pyridine, pyrimidine, pyridazine, oxadiazole, thiadiazole) or an alicyclic hydrocarbon having 3 to 12 carbon atoms (preferably cyclopentane), each of which may have 1 to 3 substituents selected from

- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);



- 4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 6) a nitro group;
- 7) a cyano group;
- 8) an amino group (e.g., amino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, methylsulfonylamino) which may be substituted by a C<sub>2-10</sub> alkanoyl group or a C<sub>1-10</sub> alkylsulfonyl group; and the like;
- ring B is pyrazole or isoxazole (preferably pyrazole), each optionally having 1 to 3 substituents selected from an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl, 1-ethylpropyl, 1-methylbutyl), an alkoxy group having 1 to 6 carbon groups (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy), an aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy), a hydroxy group, an aryl group having 6 to 14 carbon atoms (e.g., phenyl), a cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclohexyl) and the like;
- Xa is a bond or -O-;
- Xb is a bond or -O-;
- Xc is a bond or -O-;
- Ya is a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene;
- Yb is a bond;
- Yc is a bond, C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene;
- ring C is benzene optionally having 1 to 3 substituents selected from
- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine,

bromine, iodine);

3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

5 4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

6) a hydroxy group;

7) an aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy);

15 8) a cyano group;

9) a cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclohexyl); and the like; and

R is  $-OR^4$  ( $R^4$  is preferably a hydrogen atom or an alkyl group having 1 to 6 carbon atoms).

20 **[0047]**

[compound F]

A compound wherein ring A is an aromatic hydrocarbon having 6 to 14 carbon atoms (preferably benzene), a 5- or 6-membered aromatic heterocyclic ring (preferably pyridine, pyrimidine, pyridazine, oxadiazole, thiadiazole) or an alicyclic hydrocarbon having 3 to 12 carbon atoms (preferably cyclopentane), each of which may have 1 to 3 substituents selected from

1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);

30 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);

35 4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy,

ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

- 5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
- 6) a nitro group;
- 7) a cyano group;
- 8) an amino group (e.g., amino, acetylamino, propynylamino, butyrylamino, isobutyrylamino, methylsulfonylamino) which may be substituted by a C<sub>2-10</sub> alkanoyl group or a C<sub>1-10</sub> alkylsulfonyl group; and the like;

ring B is pyrazole or isoxazole (preferably pyrazole), each optionally having 1 to 3 substituents selected from an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl, 1-ethylpropyl, 1-methylbutyl), alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy), aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy), hydroxy group, aryl group having 6 to 14 carbon atoms (e.g., phenyl), cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclohexyl) and the like;

Xa is a bond or -O-;

Xb is a bond or -O-;

25 Xc is a bond or -O-;

Ya is a C<sub>1-6</sub> alkylene or C<sub>2-6</sub> alkenylene;

Yb is a bond;

Yc is a bond, a C<sub>1-6</sub> alkylene or a C<sub>2-6</sub> alkenylene;

ring C is a 5- or 6-membered monocyclic aromatic heterocyclic ring (preferably pyrazole) optionally having 1 to 3 substituents selected from

- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 2) an alkyl group having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, trifluoromethyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine,

bromine, iodine);

3) an aryl group having 6 to 14 carbon atoms (e.g., phenyl) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

5 4) an alkoxy group having 1 to 6 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, trifluoromethoxy) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

10 5) an alkylthio group having 1 to 6 carbon atoms (e.g., methylthio) which may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

6) a hydroxy group;

7) an aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy);

15 8) a cyano group;

9) a cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclohexyl); and the like; and

R is  $-OR^4$  ( $R^4$  is preferably a hydrogen atom or an alkyl group having 1 to 6 carbon atoms).

20 **[0048]**

The salt of a compound of the formula (I), (Ia), or (Ib) (hereinafter also referred to as Compound (I)) is preferably a pharmacologically acceptable salt, and is exemplified by salts with inorganic bases, salts with organic bases, salts with  
25 inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferable examples of the salts with inorganic bases include alkali metal salts such as sodium salts, potassium salts and lithium salts; alkaline earth metal salts such as  
30 calcium salts and magnesium salts; and aluminum salts and ammonium salts.

Preferable examples of the salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine,  
35 dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

Preferable examples of the salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Preferable examples of the salts with organic acids  
5 include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

Preferable examples of the salts with basic amino acids  
10 include salts with arginine, lysine, ornithine, etc.

Examples of preferable salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

**[0049]**

A prodrug of Compound (I) refers to a compound capable of  
15 being converted to Compound (I) by reactions of an enzyme, gastric juice, or the like, under physiological conditions in vivo, specifically a compound capable of being converted to Compound (I) upon enzymatic oxidation, reduction, hydrolysis, or the like, or a compound capable of being converted to  
20 Compound (I) upon hydrolysis or the like by gastric juice or the like. Examples of the prodrugs of Compound (I) include compounds derived by acylation, alkylation or phosphorylation of the amino group of Compound (I) (e.g., compounds derived by eicosanoylation, alanylation, pentylaminocarbonylation, (5-  
25 methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, tetrahydropyranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation of the amino group of Compound (I)); compounds derived by acylation, alkylation, phosphorylation or boration  
30 of the hydroxyl group of Compound (I) (e.g., compounds derived by acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation, dimethylaminomethylcarbonylation or tetrahydropyranylation of the hydroxyl group of Compound (I)); and compounds derived by  
35 esterification or amidation of the carboxyl group of Compound

(I) (e.g., compounds derived by ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, 5 phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification, or methylamidation of the carboxyl group of Compound (I)). These compounds can be produced from Compound (I) by per se known methods.

10 The prodrug of Compound (I) may be one capable of being converted to Compound (I) under physiological conditions, as described in "Iyakuhin No Kaihatsu (Development of Drugs)", vol. 7, Molecular Designing, published by Hirokawa Shoten, 1990, pages 163 - 198.

15 In addition, Compound (I) may be labeled with an isotope (e.g.,  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{35}\text{S}$ ,  $^{125}\text{I}$ ).

Furthermore, Compound (I) may be anhydrides or hydrates.

#### **【0050】**

Compounds (I) and salts thereof (hereinafter also 20 referred to as "compound of the present invention") are of low toxicity and can be used as an agent for the prophylaxis or treatment of the various diseases mentioned below in mammals (e.g., humans, mice, rats, rabbits, dogs, cats, bovines, horses, swine, monkeys), as such or in the form of 25 pharmaceutical compositions prepared by admixing with a pharmacologically acceptable carrier, etc.

#### **【0051】**

Here, the pharmacologically acceptable carriers are exemplified by various organic or inorganic carrier substances 30 in common use as materials for pharmaceutical preparations, and they are formulated as excipients, lubricants, binders, and disintegrants for solid preparations; and as solvents, solubilizers, suspending agents, isotonicizing agents, buffers, soothing agents, etc. for liquid preparations. In addition, 35 other additives for pharmaceutical preparations, such as

antiseptics, antioxidants, coloring agents, and sweetening agents, may also be used as necessary.

Preferable examples of the excipients include lactose, saccharose, D-mannitol, D-sorbitol, starch, gelatinized  
5 starch, dextrin, crystalline cellulose, low-substituted hydroxypropylcellulose, carboxymethylcellulose sodium, gum arabic, dextrin, pullulan, light silicic anhydride, synthetic aluminum silicate, and magnesium metasilicate aluminate.

Preferable examples of the lubricants include magnesium  
10 stearate, calcium stearate, talc, and colloidal silica.

Preferable examples of the binders include gelatinized starch, sucrose, gelatin, gum arabic, methylcellulose, carboxymethylcellulose, carboxymethylcellulose sodium, crystalline cellulose, saccharose, D-mannitol, trehalose,  
15 dextrin, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose, and polyvinylpyrrolidone. Preferable examples of the disintegrants include lactose, saccharose, starch, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium,  
20 carboxymethyl starch sodium, light silicic anhydride, and low-substituted hydroxypropylcellulose.

#### **【0052】**

Preferable examples of the solvents include water for injection, physiological saline, Ringer's solution, alcohol,  
25 propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil, and cottonseed oil.

Preferable examples of the solubilizers include polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol,  
30 triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, and sodium acetate.

Preferable examples of the suspending agents include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium  
35 chloride, benzethonium chloride, and monostearic glycerol;

hydrophilic polymers such as polyvinyl alcohol,  
polyvinylpyrrolidone, carboxymethylcellulose sodium,  
methylcellulose, hydroxymethylcellulose,  
hydroxyethylcellulose, and hydroxypropylcellulose; and  
5 polysorbates and polyoxyethylene-hardened castor oil.

Preferable examples of the isotonizing agents include  
sodium chloride, glycerol, D-mannitol, D-sorbitol, and  
glucose.

Preferable examples of the buffers include buffer  
10 solutions of phosphates, acetates, carbonates, citrates etc.

Preferable examples of the soothing agents include benzyl  
alcohol.

Preferable examples of the antiseptics include p-  
oxybenzoic acid esters, chlorobutanol, benzyl alcohol,  
15 phenethyl alcohol, dehydroacetic acid, and sorbic acid.

Preferable examples of the antioxidants include sulfites  
and ascorbates.

Preferable examples of the coloring agents include food  
colors such as water-soluble tar colors for food (e.g., Food  
20 Color Red Nos. 2 and 3, Food Color Yellow Nos. 4 and 5, Food  
Color Blue Nos. 1 and 2), water-insoluble lake colors (e.g.,  
aluminum salts of the aforementioned water-soluble tar colors  
for food), and natural colors (e.g.,  $\beta$ -carotene, chlorophyll,  
red oxide).

25 Preferable examples of the sweetening agents include  
saccharin sodium, dipotassium glycyrrhetinate, aspartame, and  
stevia.

Examples of the dosage forms of the pharmaceutical  
composition include oral preparations such as tablets  
30 (including sublingual tablet, orally disintegrating tablet),  
capsules (including soft capsules and microcapsules), powders,  
granules, troche, syrups; and non-oral preparations such as  
injections (e.g., subcutaneous injections, intravenous  
injections, intramuscular injections, intraperitoneal  
35 injections, drip infusions), external preparations (e.g.,



dermal preparations, ointments), suppositories (e.g., rectal suppositories, vaginal suppositories), pellets, preparations for nasal administration, preparations for transpulmonary administration (inhalant) and eye drop. These preparations may  
5 be controlled-release preparations (e.g., sustained-release microcapsule) such as rapid release preparations, sustained-release preparations and the like.

The pharmaceutical composition can be prepared by conventional methods in the fields of pharmaceutical  
10 manufacturing techniques, for example, methods described in the Japanese Pharmacopoeia. Specific production methods for oral preparations and non-oral preparations are hereinafter described in detail.

An oral preparation, for instance, is produced by  
15 adding to the active ingredient an excipient (e.g., lactose, saccharose, starch, D-mannitol), a disintegrant (e.g., carboxymethylcellulose calcium), a binder (e.g., gelatinized starch, gum arabic, carboxymethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone) or a lubricant  
20 (e.g., talc, magnesium stearate, polyethyleneglycol 6000), compression molding the obtained mixture, then, if necessary coating by a per se known method using a coating base for the purpose of taste masking, enteric coating or sustained release.

25 Examples of the coating base include a sugar coating base, a water-soluble film coating base, an enteric film coating base, a sustained-release film coating base.

As the sugar coating base saccharose is employed. Further, one or two or more species selected from talc,  
30 precipitated calcium carbonate, gelatin, gum arabic, pullulan, carnauba wax and the like may be used in combination.

Examples of the water-soluble film coating base include cellulose polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose,  
35 methylhydroxyethylcellulose; synthetic polymers such as

polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer E [Eudragit E (trademark), Rhom Pharma] and polyvinylpyrrolidone; polysaccharides such as pullulan.

Examples of the enteric film coating base include  
5 cellulose polymers such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, cellulose acetate phthalate; acrylic acid polymers such as methacrylic acid copolymer L [Eudragit L (trademark), Rhom Pharma], methacrylic acid  
10 copolymer LD [Eudragit L-30D55 (trademark), Rhom Pharma], methacrylic acid copolymer S [Eudragit S (trademark), Rhom Pharma]; natural products such as shellac and the like.

Examples of the sustained-release film coating base include cellulose polymers such as ethylcellulose; acrylic  
15 acid polymers such as aminoalkyl methacrylate copolymer RS [Eudragit RS (trademark), Rhom Pharma] and an ethyl acrylate-methyl methacrylate copolymer suspension [Eudragit NE (trademark), Rhom Pharma].

Two or more of the above coating bases may be used in  
20 admixture in an appropriate ratio. On the occasion of coating, a shading agent such as titanium oxide, red ferric oxide may be used.

Injectons are produced by dissolving, suspending or emulsifying the active ingredient in an aqueous solvent (e.g.  
25 distilled water, physiological saline, Ringer's solution) or an oleaginous solvent (e.g. vegetable oils such as olive oil, sesame oil, cotton seed oil, corn oil; propylene glycol), together with a dispersant (e.g. polysorbate 80, polyoxyethylene-hardened castor oil 60), polyethylene glycol,  
30 carboxymethylcellulose, sodium alginate), a preservative (e.g. methylparaben, propylparaben, benzyl alcohol, chlorobutanol, phenol), an isotonizing agent (e.g. sodium chloride, glycerol, D-mannitol, D-sorbitol, glucose) and the like. If desirable, additives such as a solubilizer (e.g. sodium salicylate,  
35 sodium acetate), a stabilizer (e.g. human serum albumin), a

soothing agent (e.g. benzyl alcohol), may be used.

The compound of the present invention has a hypoglycemic action, a hypolipidemic action, a hypoinsulinemic action, an insulin resistance improving action, an insulin sensitivity  
5 enhancing action, and a retinoid-related receptor function regulating action.

The term "function regulating action" used here stands for both an agonistic action and an antagonistic action.

The term "retinoid-related receptor" used here is  
10 classified as nuclear receptors, and is a DNA-binding transcription factor whose ligand is a signal molecule such as oil-soluble vitamins, etc., and may be any of a monomer receptor, a homodimer receptor and a heterodimer receptor.

Here, examples of the monomer receptor include retinoid O  
15 receptor (hereinafter, also abbreviated as ROR)  $\alpha$  (GenBank Accession No. L14611), ROR $\beta$  (GenBank Accession No. L14160), ROR $\gamma$  (GenBank Accession No. U16997); Rev-erb  $\alpha$  (GenBank Accession No. M24898), Rev-erb  $\beta$  (GenBank Accession No. L31785); ERR $\alpha$  (GenBank Accession No. X51416), ERR $\beta$  (GenBank Accession No.  
20 X51417); Ftz-FI $\alpha$  (GenBank Accession No. S65876), Ftz-FI $\beta$  (GenBank Accession No. M81385); Tlx (GenBank Accession No. S77482); GCNF (GenBank Accession No. U14666).

Examples of the homodimer receptor include homodimers formed by retinoid X receptor (hereinafter, also abbreviated  
25 as RX R)  $\alpha$  (GenBank Accession No. X52733), RXR $\beta$  (GenBank Accession No. M84820), RXR $\gamma$  (GenBank Accession No. U38480); COUP $\alpha$  (GenBank Accession No. X12795), COUP $\beta$  (GenBank Accession No. M64497), COUP $\gamma$  (GenBank Accession No. X12794); TR2 $\alpha$  (GenBank Accession No. M29960), TR2 $\beta$  (GenBank Accession No.  
30 L27586); or HNF4 $\alpha$  (GenBank Accession No. X76930), HNF4 $\gamma$  (GenBank Accession No. Z49826), etc.

Examples of the heterodimer receptor include heterodimers which are formed by the above-mentioned retinoid X receptor (RXR $\alpha$ , RXR $\beta$  or RXT $\gamma$ ) and one receptor selected from retinoid A  
35 receptor (hereinafter, also abbreviated as RAR)  $\alpha$  (GenBank

Accession No. X06614), RAR $\beta$  (GenBank Accession No. Y00291),  
RAR $\gamma$  (GenBank Accession No. M24857); thyroid hormone receptor  
(hereinafter, also abbreviated as TR)  $\alpha$  (GenBank Accession No.  
M24748), TR $\beta$  (GenBank Accession No. M26747); vitamin D receptor  
5 (VDR) (GenBank Accession No. J03258): peroxisome proliferator-  
activated receptor (hereinafter, also abbreviated as PPAR)  $\alpha$   
(GenBank Accession No. L02932), PPAR $\beta$  (PPAR $\delta$ ) (GenBank  
Accession No. U10375), PPAR  $\gamma$  (GenBank Accession No. L40904);  
LXR $\alpha$  (GenBank Accession No. U22662), LXR $\beta$  (GenBank Accession  
10 No. U14534); FXR (GenBank Accession No. U18374); MB67 (GenBank  
Accession No. L29263); ONR (GenBank Accession No. X75163); and  
NUR $\alpha$  (GenBank Accession No. L13740), NUR $\beta$  (GenBank Accession  
No. X75918) and NUR $\gamma$  (GenBank Accession No. U12767).

The compound of the present invention has an excellent  
15 ligand activity particularly to retinoid X receptors (RXR $\alpha$ ,  
RXR $\beta$ , RXR $\gamma$ ) and to peroxisome proliferator-activated receptors  
(PPAR $\alpha$ , PPAR $\beta$  (PPAR $\delta$ ), PPAR $\gamma$ ) among the above-mentioned  
retinoid-related receptors. It is useful as an agonist, a  
partial agonist, an antagonist or a partial antagonist to  
20 these receptors.

Further, the compound of the present invention has an  
excellent ligand activity to peroxisome proliferator-activated  
receptors in heterodimer receptors formed from a retinoid X  
receptor and a peroxisome proliferator-activated receptor  
25 (e.g. heterodimer receptors formed from RXR $\alpha$  and PPAR $\delta$ ,  
heterodimer receptors formed from RXR $\alpha$  and PPAR $\gamma$ ).

Accordingly, the retinoid-related receptor ligand of the  
present invention can be used advantageously as a peroxisome  
proliferator-activated receptor ligand or a retinoid X  
30 receptor ligand.

The compound of the present invention can be used as, for  
example, an agent for the prophylaxis or treatment of diabetes  
(e.g., type 1 diabetes mellitus, type 2 diabetes mellitus,  
gestational diabetes mellitus); an agent for the prophylaxis  
35 or treatment of hyperlipidemia (e.g., hypertriglyceridemia,

hypercholesterolemia, hypo-high-density-lipoproteinemia, postprandial hyperlipemia); an agent for improving insulin resistance; an agent for enhancing insulin sensitivity; an agent for the prophylaxis or treatment of impaired glucose tolerance (IGT); and an agent for preventing progress from impaired glucose tolerance to diabetes mellitus.

Regarding diagnostic criteria of diabetes mellitus, new diagnostic criteria were reported by the Japan Diabetes Society in 1999.

According to this report, diabetes mellitus is a condition wherein the fasting blood glucose level (glucose concentration in venous plasma) is not less than 126 mg/dl, the 2-hour value (glucose concentration in venous plasma) of the 75 g oral glucose tolerance test (75 g OGTT) is not less than 200 mg/dl, or the non-fasting blood glucose level (glucose concentration in venous plasma) is not less than 200 mg/dl. In addition, a condition which does not fall within the scope of the above definition of diabetes mellitus, and which is not a "condition wherein the fasting blood glucose level (glucose concentration in venous plasma) is less than 110 mg/dl or the 2-hour value (glucose concentration in venous plasma) of the 75 g oral glucose tolerance test (75 g OGTT) is less than 140 mg/dl" (normal type), is called the "borderline type".

In addition, regarding diagnostic criteria for diabetes mellitus, new diagnostic criteria were reported by ADA (American Diabetic Association) in 1997 and by WHO in 1998.

According to these reports, diabetes mellitus is a condition wherein the fasting blood glucose level (glucose concentration in venous plasma) is not less than 126 mg/dl, and the 2-hour value (glucose concentration in venous plasma) of the 75 g oral glucose tolerance test is not less than 200 mg/dl.

In addition, according to the above reports, impaired glucose tolerance is a condition wherein the fasting blood

glucose level (glucose concentration in venous plasma) is less than 126 mg/dl, and the 2-hour value (glucose concentration in venous plasma) of the 75 g oral glucose tolerance test is not less than 140 mg/dl and less than 200 mg/dl. Furthermore, according to the ADA report, a condition wherein the fasting blood glucose level (glucose concentration in venous plasma) is not less than 110 mg/dl and less than 126 mg/dl, is called IFG (impaired fasting glucose). On the other hand, according to the WHO report, a condition of IFG (impaired fasting glucose) as such wherein the 2-hour value (glucose concentration in venous plasma) of the 75 g oral glucose tolerance test is less than 140 mg/dl, is called IFG (impaired fasting glycemia).

The compound of the present invention can be used as an agent for the prophylaxis or treatment of diabetes mellitus, borderline type, impaired glucose tolerance, IFG (impaired fasting glucose) and IFG (impaired fasting glycemia) as defined by the above new diagnostic criteria. Furthermore, the compound of the present invention can also be used to prevent the progression of the borderline type, impaired glucose tolerance, IFG (impaired fasting glucose) or IFG (impaired fasting glycemia) to diabetes mellitus.

#### **【0063】**

The compound of the present invention possesses a total cholesterol lowering action and enhance a plasma anti-arteriosclerosis index  $[(\text{HDL cholesterol}/\text{total cholesterol}) \times 100]$ , and therefore, can be used as an agent for the prophylaxis or treatment of arteriosclerosis (e.g., atherosclerosis), and the like. Particularly, since the compound of the present invention concurrently has a hypoglycemic action and a total cholesterol lowering action, it is extremely useful as an agent for the prophylaxis or treatment of arteriosclerosis in diabetic patients.

The compound of the present invention can be used also as an agent for the prophylaxis or treatment of diabetic

complications (e.g., neuropathy, nephropathy, retinopathy, cataract, macroangiopathy, osteopenia, diabetic hyperosmolar coma, infectious diseases (e.g., respiratory infection, urinary tract infection, gastrointestinal tract infection, 5 dermal soft tissue infection, inferior limb infection), diabetic gangrene, xerostomia, lowered sense of hearing, cerebrovascular disease, peripheral circulatory disturbance, etc.), obesity, osteoporosis, cachexia (e.g., carcinomatous cachexia, tuberculous cachexia, diabetic cachexia, hemopathic 10 cachexia, endocrinopathic cachexia, infectious cachexia, cachexia induced by acquired immunodeficiency syndrome), fatty liver, hypertension, polycystic ovary syndrome, renal diseases (e.g., diabetic nephropathy, glomerular nephritis, glomerulosclerosis, nephrotic syndrome, hypertensive 15 nephrosclerosis, terminal renal disorder), muscular dystrophy, myocardial infarction, angina pectoris, cerebrovascular disease (e.g., cerebral infarction, cerebral apoplexy), insulin resistant syndrome, syndrome X, hyperinsulinemia, hyperinsulinemia-induced sensory disorder, tumor (e.g., 20 leukemia, breast cancer, prostate cancer, skin cancer), irritable intestine syndrome, acute or chronic diarrhea, inflammatory diseases (e.g., Alzheimer's disease, chronic rheumatoid arthritis, spondylitis deformans, osteoarthritis, lumbago, gout, postoperative or traumatic inflammation, 25 remission of swelling, neuralgia, pharyngolaryngitis, cystitis, hepatitis (including steatohepatitis such as non-alcoholic steatohepatitis), pneumonia, pancreatitis, inflammatory colitis, ulcerative colitis), visceral obesity syndrome, and the like.

30       The compound of the present invention can be used for ameliorating bellyache, nausea, vomiting, or dysphoria in epigastrium, each of which is accompanied by gastrointestinal ulcer, acute or chronic gastritis, biliary dyskinesia, or cholecystitis.

35       The compound of the present invention can control

(enhance or inhibit) appetite and food intake, and therefore, can be used as an agent for treating leanness and cibophobia (the weight increase in administration subjects suffering from leanness or cibophobia) or an agent for treating obesity.

5        Since the compound of the present invention has a  $\text{TNF-}\alpha$  suppressing effect (a  $\text{TNF-}\alpha$  production amount-lowering effect and a  $\text{TNF-}\alpha$  activity lowering effect in tissues of living organisms), the compound of the present invention can be also used as an agent for the prophylaxis or treatment of  $\text{TNF-}\alpha$   
10 mediated inflammatory diseases. Examples of such inflammatory diseases include diabetic complications (e.g., retinopathy, nephropathy, neuropathy, macroangiopathy), rheumatoid arthritis, spondylitis deformans, osteoarthritis, lumbago, gout, postoperative or traumatic inflammation, remission of  
15 swelling, neuralgia, pharyngolaryngitis, cystitis, hepatitis, pneumonia, gastric mucosal injury (including aspirin-induced gastric mucosal injury), and the like.

      The compound of the present invention has an apoptosis inhibitory activity, and can be used as an agent for the  
20 prophylaxis or treatment of diseases mediated by promotion of apoptosis. Examples of the diseases mediated by promotion of apoptosis include viral diseases (e.g., AIDS, fulminant hepatitis), neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis,  
25 retinitis pigmentosa, cerebellar degeneration), myelodysplasia (e.g., aplastic anemia), ischemic diseases (e.g., myocardial infarction, cerebral apoplexy), hepatic diseases (e.g., alcoholic hepatitis, hepatitis B, hepatitis C), joint-diseases (e.g., osteoarthritis), atherosclerosis, and the like.

30        The compound of the present invention can be used for reducing visceral fats, inhibiting accumulation of visceral fats, ameliorating glycometabolism, ameliorating lipidmetabolism, ameliorating insulin resistance, inhibiting production of oxidized LDL, ameliorating lipoprotein  
35 metabolism, ameliorating coronary artery metabolism,



preventing or treating cardiovascular complications,  
preventing or treating heart failure complications, lowering  
blood remnant, preventing or treating anovulation, preventing  
or treating hirsutism, preventing or treating  
5 hyperandrogenism, and the like.

The compound of the present invention can be used for  
secondary prevention and for inhibition in progress, of the  
various diseases described above (e.g., cardiovascular events  
such as myocardial infarction, etc.).

10       **【0065】**

Although the dose of the compound of the present  
invention varies depending on administration subject,  
administration route, target disease, clinical condition,  
etc., it is, for instance, about 0.005 to 50 mg/kg body  
15 weight, preferably 0.01 to 2 mg/kg body weight, more  
preferably 0.025 to 0.5 mg/kg body weight, as a usual dosage  
per administration for oral administration to an adult  
diabetic patient. This dose is desirably administered 1 to 3  
times a day.

20       **【0066】**

The compound of the present invention can be used in  
combination with a drug such as a therapeutic agent for  
diabetes mellitus, a therapeutic agent for diabetic  
complications, an antihyperlipidemic agent, a hypotensive  
25 agent, an antiobesity agent, a diuretic agent, a  
chemotherapeutic agent, an immunotherapeutic agent,  
antithrombotic agent, ameliorative agent for cachexia, and the  
like (hereinafter abbreviated as a combination drug). The  
combination drug may be a low molecular weight compound or a  
30 high molecular weight protein, polypeptide, antibody, vaccine  
and the like. On such occasions, the timing of administration  
of the compound of the present invention and that of the  
combination drug is not limited. They may be administered  
simultaneously or at staggered times to the administration  
35 subject. Moreover, the compound of the present invention and a

combination drug may be administered as two kinds of preparations respectively containing an active ingredient, or as a single preparation containing both active ingredients.

The dose of the combination drug can be appropriately  
5 selected based on the dose which is clinically employed. The proportion of the compound of the present invention and the combination drug can be appropriately selected according to the administration subject, administration route, target disease, clinical condition, combination, and other factors.  
10 In cases where the administration subject is human, for instance, the combination drug may be used in an amount of 0.01 to 100 parts by weight per part by weight of the compound of the present invention.

**【0067】**

15 Examples of the therapeutic agent for diabetes mellitus include insulin preparations (e.g., animal insulin preparations extracted from the bovine or swine pancreas; human insulin preparations synthesized by a genetic engineering technique using Escherichia coli or a yeast,  
20 insulin zinc; protamine zinc insulin; fragment or derivative of insulin (e.g., INS-1 and the like)), insulin resistance improving agents (e.g., pioglitazone hydrochloride, troglitazone, rosiglitazone or its maleate, GI-262570, JTT-501, MCC-555, YM-440, KRP-297, CS-011, FK-614, compounds  
25 described in WO99/58510 (e.g., (E)-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid) and the like),  $\alpha$ -glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate), biguanides (e.g., phenformin, metformin, buformin), insulin secretagogues [sulfonylureas  
30 (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, glipizide, glybuzole), repaglinide, nateglinide, mitiglinide or its calcium salt hydrate, GLP-1), dipeptidylpeptidase IV inhibitors (e.g., NVP-DPP-278, PT-100),  $\beta$ 3 agonists (e.g., CL-  
35 316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085,

AZ40140), amylin agonist (e.g., pramlintide), phosphotyrosine phosphatase inhibitors (e.g., vanadic acid), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists), SGLUT (sodium-glucose cotransporter) inhibitors (e.g., T-1095).

Examples of the therapeutic agent for diabetic complications include aldose reductase inhibitors (e.g., tolrestat, epalrestat, zenarestat, zopolrestat, minalrestat, fidarestat (SNK-860), CT-112), neurotrophic factors (e.g., NGF, NT-3, BDNF), neurotrophic factor production secretion promoter [e.g., neurotrophin production secretion promoter (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazole)-5-(3-(2-methylphenoxy)propyl)oxazole and the like) described in WO01/14372], PKC inhibitors (e.g., LY-333531), AGE inhibitors (e.g., ALT946, pimagedine, pyratoxathine, N-phenacylthiazolium bromide (ALT766), EXO-226), active oxygen scavengers (e.g. thiocctic acid), cerebral vasodilators (e.g., tiapuride, mexiletine).

Examples of the antihyperlipidemic agent include HMG-CoA reductase inhibitors (e.g., pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, cerivastatin, itavastatin, ZD-4522 or their salts (e.g., sodium salt)), fibrate compounds (e.g., bezafibrate, beclofibrate, binifibrate, cyprofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate), squalene synthase inhibitors (e.g., compound described in WO97/10224, such as N-[[ (3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic acid and the like), ACAT inhibitors (e.g., Avasimibe, Eflucimibe), anion exchange resins (e.g., cholestylamine), probuchol, nicotinic pharmaceutical agents (e.g., nicomol, niceritrol), ethyl icosapentate, phytosterol (e.g., soysterol,  $\gamma$ -oryzanol) and the like.

Examples of the hypotensive agent include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril), angiotensin II antagonists (e.g., candesartan cilexetil, losartan, eprosartan, valsartan, termisartan, 5 irbesartan, tasosartan), calcium antagonist (e.g., manidipine, nifedipine, nicardipine, amlodipine, efonidipine), potassium channel opener (e.g., levcromakalim, L-27152, AL 0671 NIP-121) and clonidine.

#### **[0069]**

10 Examples of the antiobesity agent include antiobesity drugs acting on the central nervous system (e.g. dexfenfluramine, fenfluramine, phentermine, sibutramine, anfepramon, dexamphetamine, mazindol, phenylpropanolamine, clobenzorex), pancreatic lipase inhibitors (e.g. orlistat),  $\beta$ 3 15 agonists (e.g. CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ-40140), anorectic peptides (e.g. leptin, CNTF (Ciliary Neurotrophic Factor)), cholecystokinin agonists (e.g. lintitript, FPL-15849).

Examples of the diuretic agent include xanthine 20 derivatives (e.g., theobromine and sodium salicylate, theobromine and calcium salicylate), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, 25 methyclothiazide), antialdosterone preparations (e.g., spironolactone, triamterene), carbonate dehydratase inhibitors (e.g., acetazolamide), chlorobenzenesulfonamide preparations (e.g., chlorthalidone, mefruside, indapamide), azosemide, isosorbide, ethacrynic acid, piretanide, bumetanide, 30 furosemide.

#### **[0070]**

Examples of the chemotherapeutic agent include alkylating agents (e.g., cyclophosphamide, ifosamide), metabolic antagonists (e.g., methotrexate, 5-fluorouracil or derivative 35 thereof), antitumor antibiotics (e.g., mitomycin, adriamycin),

plant-derived antitumor agents (e.g., vincristine, vindesine, Taxol), cisplatin, carboplatin, etoposide. Among these, 5-fluorouracil derivatives such as Furtulon and Neo-Furtulon are preferable.

5        Examples of the immunotherapeutic agent include microorganism- or bacterium-derived components (e.g., muramyl dipeptide derivatives, Picibanil), immunopotentiator polysaccharides (e.g., lentinan, schizophyllan, krestin), genetically engineered cytokines (e.g., interferons,  
10 interleukins (IL)), colony stimulating agents (e.g., granulocyte colony stimulating factor, erythropoietin), etc. Among these, interleukins such as IL-1, IL-2, IL-12 and the like are preferable.

As the antithrombotic agent, for example, heparin (e.g.,  
15 heparin sodium, heparin calcium, dalteparin sodium), warfarin (e.g., warfarin potassium), antithrombin agents (e.g., aragatroban), thrombolytic agents (e.g., urokinase, tisokinase, alteplase, nateplase, monteplase, pamiteplase), platelet aggregation inhibitors (e.g., ticlopidine  
20 hydrochloride, cilostazol, ethyl icosapentate, beraprost sodium, sarpogrelate hydrochloride) and the like can be mentioned.

Examples of the ameliorative agent for cachexia include cyclooxygenase inhibitors (e.g., indomethacin) (Cancer  
25 Research, vol. 49, pp. 5935-5939, 1989), progesterone derivatives (e.g., megestrol acetate) (Journal of Clinical Oncology, vol. 12, pp. 213-225, 1994), glucocorticoids (e.g. dexamethasone), metoclopramide pharmaceuticals, tetrahydrocannabinol pharmaceuticals (the above references are  
30 applied to both), fat metabolism ameliorating agents (e.g., eicosapentanoic acid) (British Journal of Cancer, vol. 68, pp. 314-318, 1993), growth hormones, IGF-1, and antibodies to the cachexia-inducing factor TNF- $\alpha$ , LIF, IL-6 or oncostatin M.

As the combination drug, nerve regeneration promoting drugs (e.g., Y-128, VX-853, prosaptide), antidepressants (e.g., desipramine, amitriptyline, imipramine), anticonvulsants (e.g., lamotrigine), antiarrhythmic drugs (e.g., mexiletine), acetylcholine receptor ligands (e.g., ABT-594), endothelin receptor antagonists (e.g., ABT-627), monoamine uptake inhibitors (e.g., tramadol), narcotic analgesics (e.g., morphine), GABA receptor agonists (e.g., gabapentine),  $\alpha 2$  receptor agonists (e.g., clonidine), local analgesics (e.g., capsaicin), protein kinase C inhibitors (e.g., LY-333531), antianxiety drugs (e.g., benzodiazepine), phosphodiesterase inhibitors (e.g., sildenafil (citrate)), dopamine agonists (e.g., apomorphine), osteoporosis therapeutic agents (e.g., alphacalcidol, calcitriol, elcatonin, salmon calcitonine, estriol, ipriflavone, pamidronate disodium hydrate, arendronate disodium, incadronate disodium), antidementia drugs (e.g., tacrine, donepezil, rivastigmine, galantamine), therapeutic agents for anischoria or polakisuria (e.g., flavoxate hydrochloride, oxybutynin hydrochloride, propiverine hydrochloride), midazolam, ketoconazole and the like can be mentioned.

#### **[0073]**

The combination drug is preferably an insulin preparation, an insulin resistance improving agent, an  $\alpha$ -glucosidase inhibitor, a biguanide, an insulin secretagogue (preferably sulfonylurea), and the like.

The above combination drugs can be used as a mixture of two or more species in an appropriate ratio. In the case of using two or more combination drugs, preferable combinations include the following.

- 1) an insulin resistance improving agent and an insulin preparation;
- 2) an insulin resistance improving agent and an insulin secretagogue;
- 3) an insulin resistance improving agent and an  $\alpha$ -

glucosidase inhibitor;

- 4) an insulin resistance improving agent and a biguanide;
- 5) an insulin preparation and a biguanide;
- 6) an insulin preparation and an insulin secretagogue;
- 5 7) an insulin preparation and an  $\alpha$ -glucosidase inhibitor;
- 8) an insulin secretagogue and an  $\alpha$ -glucosidase inhibitor;
- 9) an insulin secretagogue and a biguanide;
- 10) an insulin resistance improving agent, an insulin preparation and a biguanide;
- 10 11) an insulin resistance improving agent, an insulin preparation and an insulin secretagogue;
- 12) an insulin resistance improving agent, an insulin preparation and an  $\alpha$ -glucosidase inhibitor;
- 15 13) an insulin resistance improving agent, an insulin secretagogue and a biguanide;
- 14) an insulin resistance improving agent, an insulin secretagogue and an  $\alpha$ -glucosidase inhibitor; and
- 15 15) an insulin resistance improving agent, a biguanide and an  $\alpha$ -glucosidase inhibitor.
- 20

**【0074】**

By a combined use of the compound of the present invention and a combination drug, superior effects such as potentiation of the action of the compound of the present invention and/or the combination drug (preferably insulin preparation, insulin resistance improving agent, insulin secretagogue or biguanide), reduction of the dose of the compound of the present invention and/or the combination drug (preferably insulin resistance improving agent, insulin secretagogue or biguanide), reduction of the side effect of the compound of the present invention and/or the combination drug and the like can be obtained.

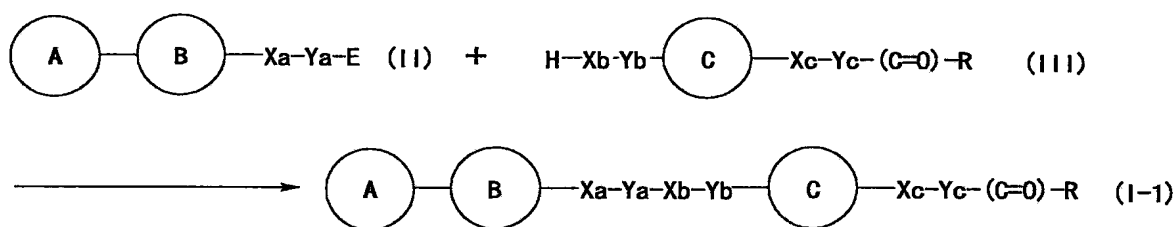
**【0075】**

The production method for the compound of the present invention is hereinafter described.

Compound (I) can be produced by a method known *per se*, such as METHODS A - I shown in the following or a method analogous thereto. In each of the following production methods, the starting material may be used in the form of a salt, and examples of such salt include those exemplified as the salts of the aforementioned compound (I).

The compound (I-1), having -O-, -S- or -NR<sup>3</sup>- (R<sup>3</sup> is as defined above) for Xb in the formula (I), can be produced by, for example, the following METHOD A.

[METHOD A]



wherein E is a leaving group, and other symbols are as defined above.

As used herein, as the leaving group represented by E, for example, a hydroxy group, a halogen atom, -OSO<sub>2</sub>R<sup>11</sup> (R<sup>11</sup> is alkyl group having 1 to 4 carbon atoms or aryl group having 6 to 10 carbon atoms which may be substituted by alkyl group having 1 to 4 carbon atoms) and the like can be mentioned.

As the alkyl group having 1 to 4 carbon atoms of the "alkyl group having 1 to 4 carbon atoms" and "aryl group having 6 to 10 carbon atoms which may be substituted by alkyl group having 1 to 4 carbon atoms" represented by R<sup>11</sup>, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and t.-butyl can be preferably mentioned, particularly preferably methyl.

As the aryl group having 6 to 10 carbon atoms of the "aryl group having 6 to 10 carbon atoms which may be substituted by alkyl group having 1 to 4 carbon atoms" represented by R<sup>11</sup>, for example, phenyl, naphthyl can be mentioned, particularly preferably phenyl.



$R^{11}$  is particularly preferably methyl, tolyl and the like.

【0076】

In this method, compound (II) and compound (III) are  
5 reacted to give compound (I-1).

When E is hydroxy group, this reaction is carried out according to a method known *per se*, such as a method described in Synthesis, page 1 (1981), or a method analogous thereto. That is, this reaction is generally carried out in the  
10 presence of an organic phosphorus compound and an electrophilic agent in a solvent which does not interfere with the reaction.

As the organic phosphorus compound, for example, triphenylphosphine, tributylphosphine and the like can be  
15 mentioned.

As the electrophilic agent, for example, diethyl azodicarboxylate, diisopropyl azodicarboxylate, azodicarbonyldipiperazine and the like can be mentioned.

The amount of the organic phosphorus compound and  
20 electrophilic agent to be used is preferably about 1 - about 5 molar equivalents relative to compound (III).

As the solvent which does not interfere with the reaction, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated  
25 hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like, and the like can be mentioned. These solvents may be used after mixing  
30 at a suitable ratio.

The reaction temperature is generally about  $-50^{\circ}\text{C}$  to about  $150^{\circ}\text{C}$ , preferably about  $-10^{\circ}\text{C}$  to about  $100^{\circ}\text{C}$ .

The reaction time is generally about 0.5-about 20 hours.

【0077】

35 When E is a halogen atom or  $-\text{OSO}_2R^{11}$ , this reaction is

carried out according to a conventional method in the presence of a base in a solvent which does not interfere with the reaction.

As the base, for example, alkali metal salts such as  
5 potassium hydroxide, sodium hydroxide, sodium hydrogen  
carbonate, potassium carbonate and the like; amines such as  
pyridine, triethylamine, N,N-dimethylaniline, 1,8-  
diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides  
such as potassium hydride, sodium hydride and the like; and  
10 alkaline metal alkoxides such as sodium methoxide, sodium  
ethoxide, potassium t.-butoxide and the like can be mentioned.

The amount of these bases to be used is preferably about  
1 - about 5 molar equivalents relative to compound (III).

As the solvent which does not interfere with the  
15 reaction, for example, aromatic hydrocarbons such as benzene,  
toluene, xylene and the like; ethers such as tetrahydrofuran,  
dioxane, diethyl ether and the like; ketones such as acetone,  
2-butanone and the like; halogenated hydrocarbons such as  
chloroform, dichloromethane and the like; amides such as N,N-  
20 dimethylformamide and the like; sulfoxides such as dimethyl  
sulfoxide and the like; and the like can be mentioned. These  
solvents may be used after mixing at a suitable ratio.

The reaction temperature is generally about -50°C to  
about 150°C, preferably about -10°C to about 100°C.

25 The reaction time is generally about 0.5-about 20 hours.

The compound (I-1) thus obtained can be isolated and  
purified by a known means of separation and purification, such  
as concentration, concentration under reduced pressure,  
solvent extraction, crystallization, recrystallization, phase  
30 transfer, chromatography and the like.

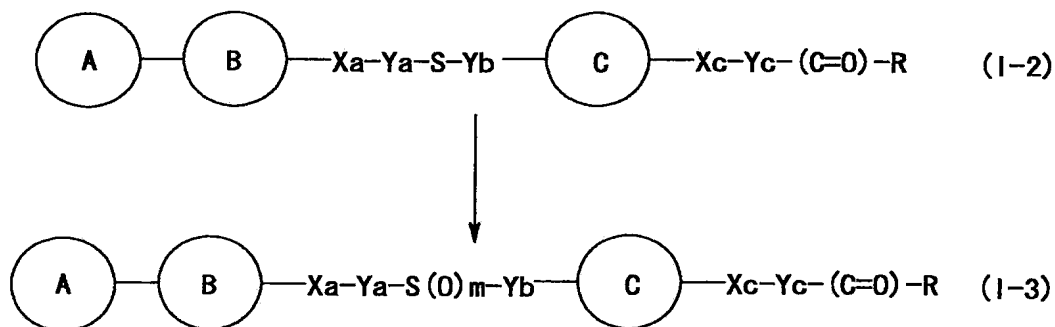
The compound (II) and compound (III) to be used as a  
starting material in the above-mentioned METHOD A can be  
produced by, for example, a method described in WO 01/38325  
and the like, or a method analogous thereto.

35 [0078]

The compound (I-3), having  $-S(O)_m-$  (m is 1 or 2) for Xb in the formula (I), can be produced by, for example, the following METHOD B.

[METHOD B]

5



wherein the symbols in the formula are as defined above.

In this method, compound (I-2) is subjected to oxidation reaction to give compound (I-3). This reaction is generally carried out using an oxidant in a solvent which does not interfere with the reaction.

As the oxidant, for example, 3-chlorophenylperbenzoic acid, sodium periodate, hydrogen peroxide, peracetic acid and the like can be mentioned.

As the solvent which does not interfere with the reaction, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; alcohols such as ethanol, methanol and the like; and the like can be mentioned. These solvents may be used after mixing at a suitable ratio.

The reaction temperature is generally about  $-50^{\circ}\text{C}$  to about  $150^{\circ}\text{C}$ , preferably about  $-10^{\circ}\text{C}$  to about  $100^{\circ}\text{C}$ .

The reaction time is generally about 0.5-about 20 hours.

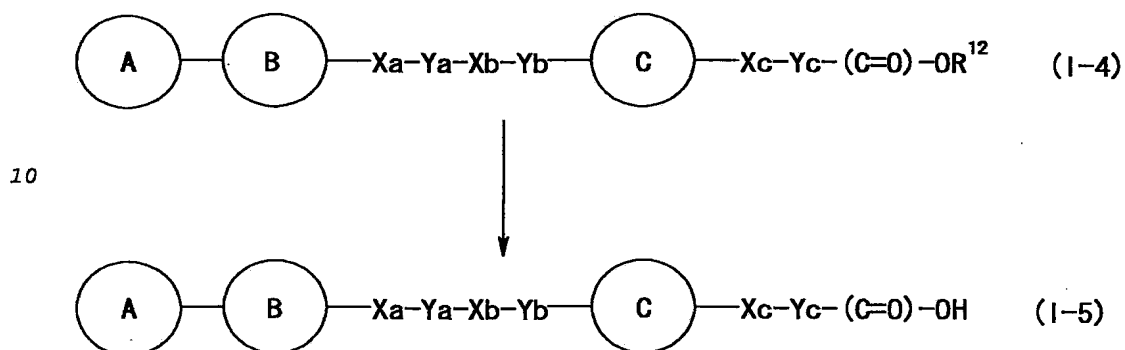
The compound (I-3) thus obtained can be isolated and purified by a known means of separation and purification, such as concentration, concentration under reduced pressure,

solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (I-2) to be used as a starting material in the above-mentioned METHOD B can be produced by, for example,  
5 the above-mentioned METHOD A.

【0079】

The compound (I-5), having -OH for R in the formula (I), can be also produced by, for example, the following METHOD C.  
[METHOD C]



wherein  $R^{12}$  is an optionally substituted hydrocarbon group, and other symbols are as defined above.

In this method, compound (I-4) is subjected to hydrolysis reaction to give compound (I-5).

15 As the "optionally substituted hydrocarbon group" represented by the above-mentioned  $R^{12}$ , those exemplified as the aforementioned  $R^4$  can be mentioned.  $R^{12}$  is preferably an alkyl group having 1 to 6 carbon atoms, more preferably methyl, ethyl and the like.

20 This reaction is carried out according to a conventional method in the presence of an acid or base in an aqueous solvent.

As the acid, for example, inorganic acids such as hydrochloric acid, sulfuric acid, hydrobromic acid and the  
25 like; organic acids such as acetic acid and the like; and the like can be mentioned.

As the base, for example, alkaline metal carbonates such as potassium carbonate, sodium carbonate and the like;

alkaline metal alkoxides such as sodium methoxide and the like; alkaline metal hydroxides such as potassium hydroxide, sodium hydroxide, lithium hydroxide and the like; and the like can be mentioned.

5       The amount of the acid or base to be used is generally an excess amount relative to compound (I-4). Preferably, the amount of the acid to be used is about 2 - about 50 equivalent amount relative to compound (I-4), and the amount of the base to be used is about 1.2 - about 5 equivalent amount relative  
10 to compound (I-4).

As the aqueous solvent, for example, a mixed solvent of water with one or more kinds of solvent selected from alcohols such as methanol, ethanol and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; dimethyl  
15 sulfoxide, acetone and the like, and the like can be mentioned.

The reaction temperature is generally about -20°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally about 0.1-about 20 hours.

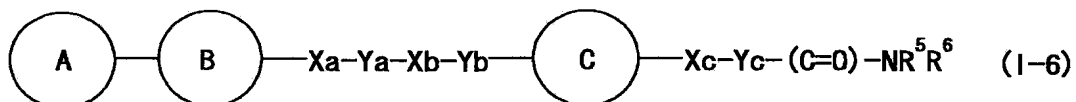
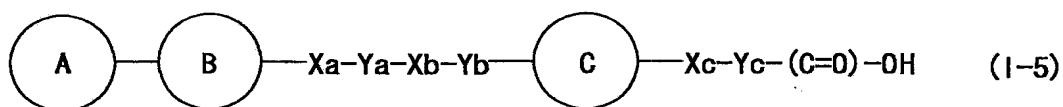
20       The compound (I-5) thus obtained can be isolated and purified by a known means of separation and purification, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

25       The compound (I-4) to be used as a starting material in the above-mentioned METHOD C can be produced by, for example, the above-mentioned METHOD A or METHOD B.

#### 【0080】

30       The compound (I-6), having  $-NR^5R^6$  ( $R^5$  and  $R^6$  are as defined above) for R in the formula (I), can be also produced by, for example, the following METHOD D.

[METHOD D]



wherein the symbols in the formula are as defined above.

In this method, compound (I-5) is subjected to amidation reaction to give compound (I-6). This reaction is carried out according to a method known *per se*, such as a method comprising direct condensation of compound (I-5) and compound (IV) using a condensing agent, a method comprising appropriate reaction of a reactive derivative of compound (I-5) with compound (IV) and the like. As used herein, as the reactive derivative of compound (I-5), for example, acid anhydrides, acid halides (e.g., acid chlorides, acid bromides), imidazolid, or mixed acid anhydride (e.g., anhydrides with methylcarbonate, ethylcarbonate, or isobutylcarbonate) and the like can be mentioned.

15      **[0081]**

As the aforementioned condensing agent, for example, generally known condensing agents such as carbodiimide condensing reagents (e.g., dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-ethyl-3-dimethylaminopropylcarbodiimide, hydrochloride thereof and the like); phosphoric acid condensing reagents (e.g., diethyl cyanophosphonate, diphenylphosphoryl azide and the like); carbonyldiimidazole, 2-chloro-1,3-dimethylimidazolium tetrafluoroborate and the like can be mentioned.

25      As the solvent to be used for the method using a condensing agent, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane

and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ethyl acetate, water and the like can be mentioned. These solvents may be used after mixing at a  
5 suitable ratio.

The amount of compound (IV) to be used is 0.1-10 molar equivalents, preferably 0.3-3 molar equivalents, relative to compound (I-5).

The amount of the condensing agent to be used is 0.1 - 10  
10 molar equivalents, preferably 0.3 - 3 molar equivalents, relative to compound (I-5).

When a carbodiimide condensing reagent such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-ethyl-3-dimethylaminopropylcarbodiimide, hydrochloride thereof and the  
15 like is used as the condensing agent, the reaction efficiency can be improved by the use of a suitable condensation promoter (e.g., 1-hydroxy-7-azabenzotriazole, 1-hydroxybenzotriazole, N-hydroxysuccinimide, N-hydroxyphthalimide and the like) as necessary. When a phosphoric acid condensing reagent such as  
20 diethyl cyanophosphonate, diphenylphosphoryl azide and the like is used as the condensing agent, the reaction efficiency can be generally improved by the addition of an organic amine base such as triethylamine and the like.

The amount of the above-mentioned condensation promoter  
25 and organic amine base is 0.1-10 molar equivalents, preferably 0.3 - 3 molar equivalents, relative to compound (I-5).

The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.5-60 hours.

#### [0082]

30 In the method using a reactive derivative of compound (I-5), for example, an acid halide is used as the reactive derivative of compound (I-5), the reaction is carried out in the presence of a base in a solvent which does not interfere with the reaction.

35 As the base, for example, amines such as triethylamine,

N-methylmorpholine, N,N-dimethylaniline and the like; alkali metal salts such as sodium hydrogen carbonate, sodium carbonate, potassium carbonate and the like; and the like can be mentioned.

5 As the solvent which does not interfere with the reaction, for example, halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like,  
10 ethyl acetate, water and the like can be mentioned. These solvents may be used after mixing at a suitable ratio.

The amount of the compound (IV) to be used is 0.1- 10 molar equivalents, preferably 0.3 - 3 molar equivalents, relative to compound (I-5).

15 The reaction temperature is generally  $-30^{\circ}\text{C}$  to  $-100^{\circ}\text{C}$ . The reaction time is generally 0.5-20 hours.

#### **【0083】**

When a mixed acid anhydride is used as the reactive derivative of compound (I-5), moreover, compound (I-5) is  
20 reacted with a chlorocarbonic ester (e.g., methyl chlorocarbonate, ethyl chlorocarbonate, isobutyl chlorocarbonate) in the presence of a base (e.g., amines such as triethylamine, N-methylmorpholine, N,N-dimethylaniline and the like; alkali metal salt such as sodium hydrogen carbonate,  
25 sodium carbonate, potassium carbonate and the like) and then reacted with compound (IV).

The amount of compound (IV) to be used is generally 0.1- 10 molar equivalents, preferably 0.3 - 3 molar equivalents, relative to compound (I-5).

30 The reaction temperature is generally  $-30^{\circ}\text{C}$  to  $100^{\circ}\text{C}$ . The reaction time is generally 0.5-20 hours.

The compound (I-6) thus obtained can be isolated and purified by a known means of separation and purification, such as concentration, concentration under reduced pressure,  
35 solvent extraction, crystallization, recrystallization, phase



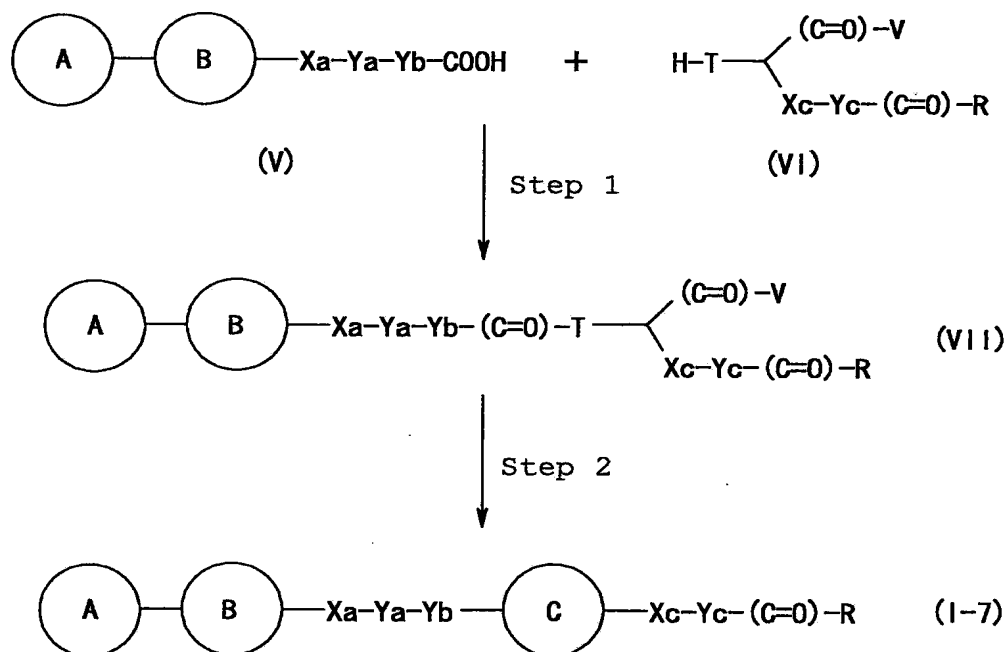
transfer, chromatography and the like.

The compound (I-5) to be used as a starting material in the above-mentioned METHOD D can be produced by, for example, the above-mentioned METHOD A -METHOD C. In addition, a known  
5 compound is used as compound (IV).

【0084】

The compound (I-7), having a bond for Xb in the formula (I), can be produced by, for example, the following METHOD E.  
[METHOD E]

10



wherein T is -O-, -S- or -NR<sup>3</sup>- (R<sup>3</sup> is as defined above), V is a hydrogen atom or a substituent, and other symbols are as  
15 defined above.

As the substituent represented by V, those exemplified as the substituent for the aforementioned ring C can be mentioned.

[Step 1]

20

This method is performed in the same manner as in the reaction between compound (I-5) and compound (IV) in the aforementioned METHOD D.

The compound (VII) thus obtained can be isolated and

purified by a known means of separation and purification, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like. It is also possible to  
5 use a reaction mixture containing compound (VII) as a starting material for Step 2, without isolating compound (VII).

The compound (V) to be used as a starting material in Step 1 of the above-mentioned METHOD E can be produced by, for example, a method described in WO 01/38325 and the like, or a  
10 method analogous thereto. The compound (VI) can be produced by a known method.

【0085】

[Step 2]

In this method, compound (VII) is subjected to ring  
15 closure reaction to give compound (I-7).

This reaction is carried out according to a conventional method in the presence of an ammonium salt in a solvent which does not interfere with the reaction.

As the ammonium salt, for example, ammonium acetate and  
20 the like can be mentioned.

The amount of the ammonium salt to be used is generally 0.1-10 molar equivalents, preferably 0.3 - 5 molar equivalents, relative to compound (VII).

As the solvent which does not interfere with the  
25 reaction, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like;  
30 alcohols such as ethanol, methanol and the like; organic acids such as acetic acid and the like; and the like can be mentioned. These solvents may be used after mixing at a suitable ratio.

The reaction temperature is generally -50°C to about  
35 200°C, preferably about -10°C to about 150°C.

The reaction time is generally about 0.5--about 20 hours.

The compound (I-7) thus obtained can be isolated and purified by a known means of separation and purification, such as concentration, concentration under reduced pressure,  
5 solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

**[0086]**

In each of the aforementioned reactions, when the starting material has an amino group, a carboxyl group, a  
10 hydroxyl group or a carbonyl group as a substituent, a protective group generally used in the peptide chemistry and the like may be introduced into these groups. After reaction, the protective group can be removed as necessary to give the object compound.

15 As the amino-protecting group, those exemplified as the aforementioned  $R^3$  can be mentioned.

As the carboxyl-protecting group, for example,  $C_{1-6}$  alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl),  $C_{7-11}$  aralkyl group (e.g., benzyl), phenyl group, trityl  
20 group, silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl),  $C_{2-6}$  alkenyl group (e.g., 1-allyl) and the like can be mentioned. These groups may be substituted by 1 to  
25 3 substituents selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine),  $C_{1-6}$  alkoxy group (e.g., methoxy, ethoxy, propoxy), nitro group and the like.

As the hydroxy-protecting group, those exemplified as the aforementioned  $R^2$  can be mentioned.

Examples of the protective groups for carbonyl include  
30 cyclic acetals (e.g., 1,3-dioxane) and non-cyclic acetals (e.g., di- $C_{1-6}$  alkyl acetals).

In addition, these protective groups can be removed by a per se known method, e.g., the method described in Protective Groups in Organic Synthesis, published by John Wiley and Sons  
35 (1980). For example, there may be used methods employing an

acid, a base, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, a trialkylsilyl halide (e.g., trimethylsilyl iodide, trimethylsilyl bromide), or the like,  
5 the reduction method, and the like.

【0087】

When compound (I) contains an optical isomer, a stereomer, a position isomer, or a rotation isomer, these isomers are also contained as Compound (I) and can each be  
10 obtained as a single substance by means of a per se known method of synthesis or separation. For example, when an optical isomer is present in Compound (I), the optical isomer separated from said compound is also included in Compound (I).

Optical isomers can be produced by a per se known method.  
15 Specifically, optical isomers are obtained by using an optically active synthesis intermediate, or optically resolving a racemate of the final product by a conventional method.

Examples of the methods of optical resolution include per  
20 se known methods, such as the fractional recrystallization method, the chiral column method, and the diastereomer method.

1) Fractional recrystallization method

A method wherein a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (-)-  
25 mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine], which salt is separated by fractional recrystallization, etc., and, if desired, subjected to a neutralization process, to yield a free optical isomer.

30 2) Chiral column method

A method wherein a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a mixture of the optical  
35 isomers to a chiral column such as ENANTIO-OVM (produced by

Tosoh Corporation) or CHIRAL series produced by DAICEL  
CHEMICAL IND., and developing it in water, various buffers  
(e.g., phosphate buffer), an organic solvent (e.g., ethanol,  
methanol, isopropanol, acetonitrile, trifluoroacetic acid,  
5 diethylamine), or a solvent mixture thereof. In the case of  
gas chromatography, for example, a chiral column such as CP-  
Chirasil-DeX CB (produced by GL Science) is used to separate  
optical isomers.

### 3) Diastereomer method

10 A method wherein a racemate mixture and an optically  
active reagent are chemically reacted to yield a diastereomer  
mixture, which is then subjected to ordinary means of  
separation (e.g., fractional recrystallization,  
chromatography) to obtain single substances, which are  
15 subjected to a chemical reaction such as hydrolysis reaction  
to cut off the optically active reagent moiety, whereby the  
desired optical isomer is obtained. For example, when Compound  
(I) has hydroxy or primary or secondary amino in the molecule  
thereof, said compound, an optically active organic acid  
20 (e.g., MTPA [ $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid],  
(-)-menthoxyacetic acid) and the like may be subjected to a  
condensation reaction to yield a diastereomer of an ester or  
amide, respectively. On the other hand, when Compound (I) has  
a carboxyl group, said compound and an optically active amine  
25 or an alcohol reagent may be subjected to a condensation  
reaction to yield a diastereomer of an amide or ester,  
respectively. The diastereomer thus separated is converted to  
an optical isomer of the original compound by subjecting it to  
an acid hydrolysis or basic hydrolysis reaction.

30 【0090】

### MODE FOR CARRYING OUT THE INVENTION

The present invention is hereinafter described in more  
detail by means of, but is not limited to, the following Test  
Examples, Reference Examples, Examples and Preparation  
35 Examples.

In addition, % in the Reference Examples and Examples below means percent by weight, unless mentioned otherwise. Room temperature means the temperature of 1 to 30°C.

Abbreviations for bases, amino acids and others used in  
5 the present specification are based on abbreviations specified by the IUPAC-IUB Commission on Biochemical Nomenclature or abbreviations in common use in relevant fields. Some examples are given below. When an optical isomer may be present in amino acid, it is of the L-configuration, unless otherwise  
10 mentioned.

The sequence numbers in the sequence listing in the present specification show the following respective sequences.

[SEQ ID NO:1]

Shows the base sequence of the primer PARD-U used in  
15 Reference Example 1a.

[SEQ ID NO:2]

Shows the base sequence of the primer PARD-L used in Reference Example 1a.

[SEQ ID NO:3]

20 Shows the base sequence of the primer XRA-U used in Reference Example 2a.

[SEQ ID NO:4]

Shows the base sequence of the primer XRA-L used in Reference Example 2a.

25 [SEQ ID NO:5]

Shows the base sequence of the primer PPRE-U used in Reference Example 5a.

[SEQ ID NO:6]

Shows the base sequence of the primer PPRE-L used in  
30 Reference Example 5a.

[SEQ ID NO:7]

Shows the base sequence of the primer TK-U used in Reference Example 5a.

[SEQ ID NO:8]

35 Shows the base sequence of the primer TK-L used in

Reference Example 5a.

[SEQ ID NO:9]

Shows the base sequence of the primer PAG-U used in  
Reference Example 6a.

5 [SEQ ID NO:10]

Shows the base sequence of the primer PAG-L used in  
Reference Example 6a.

【0092】

【Example 】

10 **Test Example 1**

Hypoglycemic and hypolipidemic actions in mice

Test compounds were mixed in a powdery diet (CE-2, Japan  
Clea) at the concentration of 0.005 %, and freely given to KKA<sup>y</sup>  
mice (9 to 12 weeks old, 5 mice in a group), a model of obese  
15 and non-insulin dependent diabetes mellitus (type 2 diabetes  
mellitus), for four days. During this period, water was given  
freely. Blood was sampled from orbital venous plexus, and  
glucose and triglyceride levels in plasma separated from blood  
were determined enzymatically using L type Wako Glu2 (Wako  
20 Pure Chemical Industries, Ltd.) or L type Wako TG-H (Wako Pure  
Chemical Industries, Ltd.), respectively. The results are  
given in Table 1.

In the table, "hypoglycemic action (%)" means the rate of  
decrease (%) in the blood glucose level of the treated group  
25 when the blood glucose level of the non-treated group is taken  
as 100%. In addition, the "hypolipidemic action (%)" means the  
rate of decrease (%) in the blood triglyceride level of the  
treated group when the blood triglyceride level of the non-  
treated group is taken as 100%.

30

Table 1

Test compound (Example No.)	Hypoglycemic action (%)	Hypolipidemic action (%)
28	42	56
29	46	65
30	35	58
31	50	69
34	49	77
35	30	32
41	25	48
42	32	19
179	34	37
180	32	36
181	49	49
185	47	43
189	50	38
197	45	65
207	49	72
212	52	55
213	51	52
214	44	52
215	50	45
216	46	61
217	34	18
218	34	43
220	44	50
221	46	21
222	36	54
223	38	55
224	48	60
225	31	35
227	43	26
229	41	49
235	43	64
239	42	65
241	38	27
245	42	55
247	25	34
253	49	35
259	34	70
260	42	44
272	48	69
274	50	60
300	36	39
305	50	55
311	52	29
313	51	48
315	53	70
337	44	48
339	50	54
340	49	55

These results indicated that the compounds of the present invention possess excellent hypoglycemic and hypolipidemic



actions, and are proved to be useful as agents for preventing or treating diabetes mellitus, hyperlipidemia (especially hypertriglyceridemia), impaired glucose tolerance, etc.

【0093】

5 **Test Example 2**

Plasma anti-arteriosclerosis index-enhancing action in mice

Test compounds were mixed in a powdery diet (CE-2, Japan Clea) at the concentration of 0.005%, and freely given to KKA<sup>y</sup> mice (9 to 12 weeks old, 5 mice per group), a model of obese  
10 and non-insulin dependent diabetes mellitus (type 2 diabetes mellitus), for four days. During this period, water was given freely. Blood was sampled from orbital venous plexus and components in plasma separated from blood were determined. Total cholesterol levels were determined by using L type Wako  
15 Cholesterol (Wako Pure Chemical Industries, Ltd.). Precipitation reagent for HDL cholesterol (Wako Pure Chemical Industries, Ltd.) was added to a part of the plasma to precipitate non-HDL lipoprotein, and cholesterol (HDL cholesterol) in the resulting supernatant was determined. The  
20 plasma anti-arteriosclerosis index [(HDL cholesterol/total cholesterol)×100] was calculated by using these cholesterol levels. The results are given in Table 2.

In the Table, "Plasma anti-arteriosclerosis index-enhancing action (%)" represents the percent increase (%) of  
25 plasma anti-arteriosclerosis index in the treatment group, when the plasma anti-arteriosclerosis index in the non-treatment group is taken as 100%.

Table 2

Test compound (Example No.)	Plasma anti- arteriosclerosis index- enhancing action (%)
22	12
28	18
29	23
30	19
31	16
34	20
35	14
41	12
185	15
189	20
223	12
224	14
225	12
253	16
259	25
260	22
274	11
299	11
300	12
302	24
303	14
304	13
305	22
313	15
315	11
316	10
318	22
322	14
332	11
333	11
335	12
337	24
339	22
340	21

These results indicated that the compounds of the present invention possess excellent total cholesterol lowering  
5 actions, and are proved to be useful as agents for preventing or treating hyperlipidemia (especially hypercholesterolemia). Additionally, the compounds of the present invention possess excellent plasma anti-arteriosclerosis index-enhancing actions, and are proved to be useful as an agent for the  
10 prophylaxis or treatment of hyperlipidemia (especially hypo-HDL-cholesterolemia), arteriosclerosis, etc.

【0094】

### Test Example 3

(PPAR $\gamma$ -RXR $\alpha$  heterodimer ligand activity)

A PPAR $\gamma$ : RXR $\alpha$ : 4ERPP/CHO-K1 cells obtained in Reference Example 8a described later were cultured in HAM F12 medium  
5 (produced by Life Technologies, Inc., USA) containing 10% Fetal bovine serum (produced by Life Technologies, Inc., USA) and then inoculated to a 96-well white plate (produced by Corning Costar Corporation, USA) at the density of  $2 \times 10^4$  cells/well, and cultured in a CO<sub>2</sub> gas incubator at 37°C  
10 overnight.

After removing the medium from 96 well white plate, 80  $\mu$ l of HAM F12 medium containing 0.1% fatty acid-free bovine serum albumin (BSA) and 20  $\mu$ l of test compound were added, which was cultured in a CO<sub>2</sub> gas incubator at 37°C for 18-48 hours. After  
15 removing the medium, 40  $\mu$ l of PIKKAGENE 7.5 (produced by Wako Pure Chemical Industries, Ltd.) diluted twice with HBSS (HANKS' BALANCED SALT SOLUTION) (produced by BIO WHITTAKER Inc., USA), was added. After stirring, the luciferase activity was determined using 1420 ARVO Multilabel Counter (produced by  
20 PerkinElmer Inc., USA).

A fold induction was calculated based on the luciferase activity of each test compound by taking the luciferase activity in the non-treatment group as 1. The values of the test compound concentration and the fold induction were  
25 analyzed using PRISM (produced by GraphPad Software Inc. USA) to calculate the EC<sub>50</sub> values, the effective concentration of a test compound for 50% of the maximum fold induction. The results are shown in Table 3.

30

Table 3

Test compound (Example No.)	EC <sub>50</sub> (nM)
24	38
28	35
29	160
30	210
31	35
41	77
42	19
43	53
58	43
77	21
98	110
104	34
116	82
125	26
137	35
181	75
189	14
196	42
197	22
198	30
201	63
210	16
212	13
213	7.8
214	18
215	20
216	18
218	51
220	9.6
221	12
227	22
229	21
235	26
237	17
239	35
259	76
270	99
271	30
272	50
273	90
274	82
277	36
302	37
303	52
304	40
306	17
307	23
315	35
316	3.8
319	26
332	29
333	61
334	74

These results indicated that the compounds of the present invention have potent PPAR $\gamma$ -RXR $\alpha$  heterodimer ligand activity.

【0095】

5 **Test example 4**

(PPAR $\delta$ -RXR $\alpha$  heterodimer ligand activity)

The transformant obtained in Reference Example 9a was suspended in DMEM medium (produced by Life Technologies, Inc., USA) containing 0.1% fatty acid-free bovine serum albumin  
10 (BSA) (produced by Wako Pure Chemical Industries, Ltd.), and inoculate to each well of a 96-well white plate (produced by Corning Costar Corporation, USA) by 80  $\mu$ l at  $1 \times 10^4$  cells/well. Then the test compound (20  $\mu$ l) was added and cultured at 37°C under 5% CO<sub>2</sub> for 36-48 hours. After removing the medium from  
15 the 96-well white plate, 40  $\mu$ l of PIKKAGENE LT 7.5 (produced by Wako Pure Chemical Industries, Ltd.) diluted twice with HBSS (HANKS' BALANCED SALT SOLUTION) (produced by BIO WHITTAKER Inc., USA), was added. After stirring, the luciferase activity was determined using 1420 ARVO Multilabel Counter (produced by  
20 PerkinElmer Inc., USA).

A fold induction was calculated based on the luciferase activity of each test compound by taking the luciferase activity in the non-treatment group as 1. The values of the test compound concentration and the fold induction were  
25 analyzed using PRISM (produced by GraphPad Software Inc. USA) to calculate the EC<sub>50</sub> values, the effective concentration of a test compound for 50 % of the maximum fold induction. The results are shown in Table 4.

30

Table 4

Test compound (Example No.)	EC <sub>50</sub> (nM)
22	8.6
24	9.3
30	2.6
31	9.6
34	8.1
35	1.6

42	1.9
43	3.7
44	3.9
46	6.4
49	1.7
51	3.9
56	2.8
58	1.9
59	9.7
62	0.81
63	9.5
65	1.8
75	3.8
76	1.9
85	6.0
86	1.5
91	6.0
92	1.9
94	4.0
96	1.7
98	1.2
99	0.55
102	9.1
104	7.0
105	7.2
110	4.6
111	6.1
113	4.8
116	0.6
117	1.6
118	7.2
122	4.9
123	2.9
124	2.4
125	1.5
126	2.2
127	3.9
129	4.9
131	2.7
137	9.6
146	5.8
150	2.7
152	9.9
153	1.9
154	1.5
155	3.8
157	4.7
168	1.6
169	5.7
182	5.6
186	1.9
189	2.1
200	5.9
201	1.2
204	4.6
213	8.3
237	6.1

255	9.5
258	5.5
278	6.0
279	5.1
304	5.7
316	9.9
319	5.1

These results indicated that the compounds of the present invention have potent PPAR $\delta$ -RXR $\alpha$  heterodimer ligand activity.

【0096】

#### 5 **Reference Example 1a**

(Human PPAR $\delta$  gene cloning)

A human PPAR $\delta$  gene was cloned using a pancreas cDNA (produced by Toyobo Co., Ltd., trade name: QUICK-Clone cDNA) as a template by means of a PCR method employing a primer set  
 10 shown below which was prepared with reference to the base sequence of PPAR $\delta$  gene reported by Schmidt, A. et al (Mol. Endocrinol., 1992, Vol. 6, page 1634 - 1641).

PARD-U; 5'-AAC GGT ACC TCA GCC ATG GAG CAG CCT CAG GAG G-3'

(Sequence ID Number: 1)

15 PARD-L; 5'-TAA GTC GAC CCG TTA GTA CAT GTC CTT GTA GAT C-3'

(Sequence ID Number: 2)

The PCR reaction was performed by Hot Start method using AmpliWax PCR Gem 100 (produced by TAKAEA SHUZO CO., LTD.). First, 2  $\mu$ l of 10 $\times$ LA PCR Buffer, 3  $\mu$ l of 2.5 mM dNTP solution,  
 20 2.5  $\mu$ l each of 12.5  $\mu$ M primer solutions and 10  $\mu$ l of sterilized distilled water were mixed to obtain a bottom layer solution mixture. 1  $\mu$ l of human heart cDNA (1 Ng/ml) as a template, 3  $\mu$ l of 10 $\times$ LA PCR Buffer, 1  $\mu$ l of 2.5 mM dNTP solution, 0.5  $\mu$ l of TaKaRa LA Taq DNA polymerase (produced by TAKARA SHUZO CO.,  
 25 LTD.) and 24.5  $\mu$ l of sterilized distilled water were mixed to obtain a top layer solution mixture.

To the prepared bottom layer solution mixture, added was one unit of AmpliWax PCR Gem 100 (produced by TAKARA SHUZO CO., LTD.), which was treated at 70°C for 5 minutes and then in  
 30 ice for 5 minutes. Then, the top layer solution mixture was added to the mixture to prepare the reaction mixture of PCR. A

tube containing the reaction mixture was set on a thermal  
cycler (produced by Perkin Elmer, USA) and treated at 95°C for  
2 minutes. After repeating the cycle of 95°C for 15 seconds  
and 68°C for 2 minutes a further 45 times, the tube was treated  
5 at 72°C for 8 minutes.

The PCR product thus obtained was subjected to  
electrophoresis on agarose gel (1%), and 1.4 kb DNA fragment  
containing PPAR $\delta$  gene was recovered from the gel, and then  
inserted into pT7 Blue-T vector (produced by TAKARA SHUZO CO.,  
10 LTD.) to obtain a plasmid pTBT-hPPAR $\delta$ .

### Reference Example 2a

(Human RXR $\alpha$  gene cloning)

A human RXR $\alpha$  gene was cloned using a kidney cDNA  
(produced by Toyobo Co., Ltd., trade name: QUICK-Clone cDNA)  
15 as a template by means of a PCR method employing a primer set  
shown below which was prepared with reference to the base  
sequence of RXR $\alpha$  gene reported by Mangelsdorf, D. J. et al  
(Nature, 1990, Vol. 345 (6272), page 224 - 229).

XRA-U: 5'-TTA GAA TTC GAC ATG GAC ACC AAA CAT TTC CTG-3'

20 (Sequence ID Number: 3)

XRA-L: 5'-CCC CTC GAG CTA AGT CAT TTG GTG CGG CGC CTC-3'

(Sequence ID Number: 4)

The PCR reaction was performed by Hot Start method using  
AmpliWax PCR Gem 100 (produced by TAKARA SHUZO CO., LTD.).  
25 First, 2  $\mu$ l of 10 $\times$ LA PCR Buffer, 3  $\mu$ l of 2.5 mM dNTP solution,  
2.5  $\mu$ l each of 12.5  $\mu$ M primer solutions and 10  $\mu$ l of sterilized  
distilled water were mixed to obtain a bottom layer solution  
mixture. 1  $\mu$ l of human kidney cDNA (1 ng/ml) as a template, 3  
 $\mu$ l of 10 $\times$ LA PCR Buffer, 1  $\mu$ l of 2.5 mM dNTP solution, 0.5  $\mu$ l of  
30 TaKaRa LA Taq DNA polymerase (produced by TAKARA SHUZO CO.,  
LTD.) and 24.5  $\mu$ l of sterilized distilled water were mixed to  
obtain a top layer solution mixture.

To the bottom layer solution mixture described above,  
added was one unit of AmpliWax PCR Gem 100 (produced by TAKARA  
35 SHUZO CO., LTD.), which was treated at 70°C for 5 minutes and



then in ice for 5 minutes. Then, the top layer solution mixture was added to the mixture to prepare the reaction mixture of PCR. A tube containing the reaction mixture was set on a thermal cycler (produced by Perkin Elmer, USA) and  
5 treated at 95°C for 2 minutes. After repeating the cycle of 95°C for 15 seconds and 68°C for 2 minutes a further 35 times, the tube was treated at 72°C for 8 minutes.

The PCR product thus obtained was subjected to electrophoresis on agarose gel (1%), and 1.4 kb DNA fragment  
10 containing RXR $\alpha$  gene was recovered from the gel, and then inserted into pT7 Blue-T vector (produced by TAKARA SHUZO CO., LTD.) to obtain a plasmid pTBT-hRXR $\alpha$ .

【0097】

**Reference Example 3a** (Construction of plasmids for expressing  
15 Human PPAR $\delta$ )

pCI vector (produced by Promega, USA) was digested with BamHI (produced by TAKARA SHUZO CO., LTD.) and then treated with T4 DNA polymerase (produced by TAKARA SHUZO CO., LTD.) to obtain a blunt terminal. On the other hand, pGFP-C1 (produced  
20 by Toyobo Co., Ltd.) was digested with Bsu36I (produced by Daiichi Pure Chemicals CO., LTD.) and then treated with T4 DNA polymerase (produced by TAKARA SHUZO CO., LTD.) to form a blunt terminal, the both DNA fragments were ligated using DNA Ligation kit (produced by TAKARA SHUZO CO., LTD.) to obtain  
25 the plasmid pMCMVneo. A 5.6 Kb KpnI-SalI fragment of plasmid pMCMVneo was ligated to a 1.3 kb KpnI-SalI fragment containing hPPAR $\delta$  gene of plasmid pTBT-hPPAR $\delta$  described in Reference Example 1a to construct a plasmid pMCMVneo-hPPAR $\delta$ .

【0098】

30 **Reference Example 4a** (Construction of plasmids for expressing Human RXRa)

A 5.6Kb EcoRI-SalI fragment of plasmid pMCMVneo described in Reference Example 3a was ligated to a 1.4kb EcoRI-XhoI fragment containing hRXRa gene of plasmid pTBT-hRXRa described  
35 in Reference Example 2a to prepare plasmid pMCMVneo-hRXRa.

【0099】

### Reference Example 5a

(Construction of reporter plasmids)

A DNA fragment containing PPAR-responding element (PPRE)  
5 of an acyl CoA oxidase was prepared using the following 5'-  
terminal phosphorylated synthetic DNA.

PPRE-U: 5'-pTCGACAGGGGACCAGGACAAAGGTCACGTTCTGGGAG-3' (Sequence  
ID Number: 5)

PPRE-L: 5'-pTCGACTCCCGAACGTGACCTTTGTCCTGGTCCCCTG-3' (Sequence  
10 ID Number: 6)

First, PPRE-U and PPRE-L were annealed and inserted to  
Sal I site of plasmid pBlue Script SK+. By determining the  
base sequence of the inserted fragment, plasmid pBSS-PPRE4 in  
which 4 PPREs were ligated in tandem was selected.

15 A HSV thymidine kinase minimum promoter (TK promoter)  
region was cloned using pRL-TK vector (produced by Promega,  
USA) as a template by means of a PCR method employing a primer  
set shown below which was prepared with reference to the base  
sequence of the promoter region of thymidine kinase reported  
20 by Luckow, B et al (Nucleic Acids Res., 1987, Vol. 15 (13),  
p.5490)

TK-U: 5'-CCCAGATCTCCCCAGCGTCTTGTTCATTG-3' (Sequence ID Number:  
7)

TK-L: 5'-TCACCATGGTCAAGCTTTTAAGCGGGTC-3' (Sequence ID Number:  
25 8)

The PCR reaction was performed by Hot Start method using  
AmpliWax PCR Gem 100 (TAKARA SHUZO CO., LTD.). First, 2  $\mu$ l of  
10 $\times$ LA PCR Buffer, 3  $\mu$ l of 2.5 mM dNTP solution, 2.5  $\mu$ l each of  
12.5  $\mu$ M primer solutions and 10  $\mu$ l of sterilized distilled  
30 water were mixed to obtain a bottom layer solution mixture. 1  
 $\mu$ l of pRL-TK vector (produced by Promega, USA) as a template, 3  
 $\mu$ l of 10 $\times$ LA PCR Buffer, 1  $\mu$ l of 2.5 mM dNTP solution, 0.5  $\mu$ l of  
TaKaRa LA Taq DNA polymerase (produced by TAKARA SHUZO CO.,  
LTD.) and 24.5  $\mu$ l of sterilized distilled water were mixed to  
35 obtain a top layer solution mixture.

To the bottom layer solution mixture described above, added was one unit of AmpliWax PCR Gem 100 (produced by TAKARA SHUZO CO., LTD.), which was treated at 70°C for 5 minutes and then in ice for 5 minutes. Then, the top layer solution  
5 mixture was added to the mixture to prepare the reaction mixture of PCR. A tube containing the reaction mixture was set on a thermal cycler (produced by Perkin Elmer, USA) and treated at 95°C for 2 minutes. After repeating the cycle of 95°C for 15 seconds and 68°C for 2 minutes a further 35 times,  
10 the tube was treated at 72°C for 8 minutes.

The PCR product thus obtained was subjected to electrophoresis on agarose gel (1%), and 140 b DNA fragment containing TK promoter was recovered from the gel, and then inserted into pT7 Blue-T vector (produced by TAKARA SHUZO CO.,  
15 LTD.). By digesting the plasmid thus obtained with the restriction enzymes Bgl II and NcoI, a fragment containing TK promoter was obtained, which was ligated to the Bgl II-NcoI fragment of plasmid pGL3-Basic vector (produced by Promega, USA) to obtain plasmid pGL3-TK.

20 A 4.9 kb NheI-XhoI fragment of plasmid pGL3-TK thus obtained was ligated to a 200 bp NheI-XhoI fragment of plasmid pBSS-PPRE4 to obtain plasmid pGL3-4ERPP-TK.

This plasmid pGL3-4ERPP-TK was digested with BamHI (produced by TAKARA SHUZO CO., LTD.) and then treated with  
25 T4DNA polymerase (produced by TAKARA SHUZO CO., LTD.) to form a blunt terminal, whereby obtaining a DNA fragment.

On the other hand, pGFP-C1 (produced by Toyobo Co., Ltd.) was digested with Bsu36I (NEB) and then treated with T4DNA polymerase (produced by TAKARA SHUZO CO., LTD.) to form a  
30 blunt terminal, whereby obtaining a 1.6 kb of a DNA fragment. The both DNA fragments were ligated to construct a reporter plasmid pGL3-4ERPP-TK neo.

【0100】

#### Reference Example 6a

35 (Human PPAR $\gamma$  gene cloning)

A human PPAR $\gamma$  gene was cloned using a heart cDNA (produced by Toyobo Co., Ltd., trade name: QUICK-Clone cDNA) as a template by means of a PCR method employing a primer set shown below which was prepared with reference to the base sequence of PPAR $\gamma$  gene reported by Greene et al (Gene Expr., 5 1995, Vol.4 (4-5), page 281 - 299).

PAG-U: 5'-GTG GGT ACC GAA ATG ACC ATG GTT GAC ACA GAG-3'

(Sequence ID Number: 9)

PAG-L: 5'-GGG GTC GAC CAG GAC TCT CTG CTA GTA CAA GTC-3'

10 (Sequence ID Number: 10)

The PCR reaction was performed by Hot Start method using AmpliWax PCR Gem 100 (produced by TAKARA SHUZO CO., LTD.). First, 2  $\mu$ l of 10 $\times$ LA PCR Buffer, 3  $\mu$ l of 2.5 mM dNTP solution, 2.5  $\mu$ l each of 12.5  $\mu$ M primer solutions and 10  $\mu$ l of sterilized 15 distilled water were mixed to obtain a bottom layer solution mixture. 1  $\mu$ l of human heart cDNA (1 ng/ml) as a template, 3  $\mu$ l of 10 $\times$ LA PCR Buffer, 1  $\mu$ l of 2.5 mM dNTP solution, 0.5  $\mu$ l of TaKaRa LA Taq DNA polymerase (produced by TAKARA SHUZO CO., LTD.) and 24.5  $\mu$ l of sterilized distilled water were mixed to 20 obtain a top layer solution mixture.

To the bottom layer solution mixture described above, added was one unit of AmpliWax PCR Gem 100 (produced by TAKARA SHUZO CO., LTD.), which was treated at 70°C for 5 minutes and then in ice for 5 minutes. Then the top layer solution mixture 25 was added to the mixture to prepare the reaction mixture of PCR. A tube containing the reaction mixture was set on a thermal cycler (produced by Perkin Elmer, USA) and treated at 95°C for 2 minutes. After repeating the cycle of 95°C for 15 seconds and 68°C for 2 minutes a further 35 times, the tube was 30 treated at 72°C for 8 minutes.

The PCR product thus obtained was subjected to electrophoresis on agarose gel (1%), and 1.4 kb DNA fragment containing PPAR $\gamma$  gene was recovered from the gel, and then inserted into pT7 Blue-T vector (produced by TAKARA SHUZO CO., 35 LTD.) to obtain a plasmid pTBT-hPPAR $\gamma$ .

【0101】

**Reference Example 7a**

(Construction of plasmids for expressing Human PPAR $\gamma$ , RXR $\alpha$ )

A 7.8 kb FspI-NotI fragment of plasmid pVgRXR (produce by  
5 Invitrogen, USA) was ligated to a 0.9 kb FspI-NotI fragment  
containing RXR $\alpha$  gene of plasmid pTBT-hRXR $\alpha$  obtained in  
Reference Example 2a to prepare plasmid pVgRXR2. Then, pVgRXR2  
was digested with BstXI and then treated with T4DNA polymerase  
(produced by TAKARA SHUZO CO., LTD.) to obtain a blunt  
10 terminal. Then digestion at KpnI gave a 6.5 kb DNA fragment.  
On the other hand, plasmid pTBT-hPPAR $\gamma$  obtained in Reference  
Example 6a was digested with Sal I and then treated with T4DNA  
polymerase (produced by TAKARA SHUZO CO., LTD.) to obtain a  
blunt terminal. Then digestion at KpnI gave a 1.4 kb DNA  
15 fragment containing human PPAR $\gamma$  gene.

The both DNA fragments were ligated to construct plasmid  
pVgRXR2-hPPAR $\gamma$ .

【0102】

**Reference Example 8a**

20 (Introduction of plasmids for expressing Human PPAR $\gamma$  and RXR $\alpha$ ,  
and reporter plasmid into CHO-K1 cell and establishment of  
expressed cell)

After a CHO-K1 cell cultured in a 150cm<sup>2</sup> cell culture  
flask (750 ml) (produced by Corning Costar Corporation, USA)  
25 containing HAM F12 medium (produced by Life Technologies,  
Inc., USA) supplemented with 10% Fetal Bovine Serum (produced  
by Life Technologies, Inc., USA) was scraped by treating with  
0.5 g/L trypsin-0.2 g/L EDTA (ethylenediaminetetraacetic acid)  
(produced by Life Technologies, Inc., USA), the cell was  
30 washed with PBS (phosphate-buffered saline) (produced by Life  
Technologies, Inc., USA), centrifuged (1000 rpm, 5 minutes),  
and then suspended in PBS. Subsequently, a DNA was introduced  
into the cell under the condition shown below using GENE  
PULSER (produced by Bio-Rad Laboratories, USA).

35 Namely, to a cuvette having a 0.4 cm gap, added were

8x10<sup>6</sup> cells and 10 µg of plasmid pVgRXR2-hPPAR<sub>γ</sub> obtained in Reference Example 7a and 10 µg of reporter plasmid pGL3-4ERPP-TK neo obtained in Reference Example 5a, which was subjected to electroporation at the voltage of 0.25 kV under the  
5 capacitance of 960 µF. Subsequently, the cell was transferred into a HAM F12 medium containing 10% Fetal Bovine Serum and cultured for 24 hours and then the cell was scraped again and centrifuged, and then suspended in HAM F12 medium containing  
10 10% Fetal Bovine Serum supplemented with 500 µg/ml of GENETICIN (produced by Life Technologies, Inc., USA) and 250 µg/ml of ZEOCIN (produced by Invitrogen, USA). The obtained suspension was diluted to the density of 10<sup>4</sup> cells/ml and inoculated to a 96-well plate (produced by Corning Costar Corporation, USA), which was cultured in a CO<sub>2</sub> gas incubator at 37°C, whereby  
15 obtaining a GENETICIN- and ZEOCIN-resistant transformant.

Subsequently, after the transformant cell line thus obtained was cultured in a 24-well plate (produced by Corning Costar Corporation, USA), selected was a cell line in which the luciferase was expressed and induced, i.e.,  
20 PPAR<sub>γ</sub>:RXR<sub>α</sub>:4ERPP/CHO-K1 cell by addition of 10 µM of pioglitazone hydrochloride.

【0103】

#### Reference Example 9a

(Introduction of plasmids for expressing Human PPAR<sub>δ</sub> and RXR<sub>α</sub>,  
25 and reporter plasmid into COS-1 cell and establishment of transformant)

COS-1 cells were inoculated to a 150cm<sup>2</sup> cell culture flask (produced by Corning Costar Corporation, USA) at the density of 5x10<sup>6</sup> cells/50 ml, and cultured at 37°C under 5%CO<sub>2</sub>  
30 conditions for 24 hours. Subsequently, a DNA was introduced into the cell under the condition shown below using Lipofectamine (produced by Invitrogen, USA).

First, Lipofectamine (125 µl), PLUS Reagent (100 µl, produced by Invitrogen, USA), plasmid pMCMVneo-hPPAR<sub>δ</sub> (2.5 µg)  
35 obtained in Reference Example 3a, plasmid pMCMVneo-hRXR<sub>α</sub> (2.5

μg) obtained in Reference Example 4a and reporter plasmid pGL3-4ERPP-TK neo (5 μg) obtained in Reference Example 5a, and pRL-tk (5 μg, produced by Promega, USA) were mixed with opti-MEM (5 ml, produced by Invitrogen, USA) to give a transfection

5 mixture.

Then, the above-mentioned transfection mixture and opti-MEM (20 ml) were added to COS-1 cells washed with opti-MEM, and the cells were cultured at 37°C under 5% CO<sub>2</sub> conditions for 3 hours. DMEM medium (25 ml, produced by Life Technologies, Inc., USA) containing 0.1% fatty acid-free bovine serum albumin (BSA) (produced by Wako Pure Chemical Industries, Ltd.) was added to the obtained COS-1 cells, and the cells were cultured at 37°C under 5% CO<sub>2</sub> conditions for 18-24 hours to give a transformant.

15     **[0104]**

#### **Reference Example 1**

To a mixture of N-hydroxy-4-(trifluoromethyl)benzenecarboximidoyl chloride (11.00 g), 4-pentyn-1-ol (4.98 g) and tetrahydrofuran (150 ml) was dropwise added a solution (10 ml) of triethylamine (10 ml) in tetrahydrofuran at 0°C and the mixture was stirred at room temperature overnight. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-propanol (10.68 g, yield 80%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 59-60°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.41 (1H, br t), 1.92-2.14 (2H, m), 2.88-3.05 (2H, m), 3.68-3.86 (2H, m), 6.37 (1H, s), 7.66-7.76 (2H, m), 7.87-7.97 (2H, m).

35     **Reference Example 2**

To a mixture of 3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-propanol (9.68 g), triethylamine (6.5 ml) and ethyl acetate (150 ml), was dropwise added a solution (10 ml) of methanesulfonyl chloride (3.3 ml) in ethyl acetate at 0°C and the mixture was stirred at room temperature overnight. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate and then saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-propyl methanesulfonate (11.78 g, yield 94%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.96-2.10 (2H, m), 2.86-2.96 (2H, m), 3.16 (3H, s), 4.24-4.34 (2H, m), 6.36 (1H, s), 7.65-7.76 (2H, m), 7.86-7.97 (2H, m).

### Reference Example 3

A mixture of 3-hydroxy-1-phenyl-1H-pyrazole-5-carboxylic acid (29.55 g), benzyl bromide (35 ml), potassium carbonate (40.99 g) and N,N-dimethylformamide (300 ml) was stirred overnight at 90°C. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and benzyl 3-benzyloxy-1-phenyl-1H-pyrazole-5-carboxylate (51.33 g, yield 92%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.20 (2H, s), 5.27 (2H, s), 6.49 (1H, s), 7.18-7.47 (15H, m).

【0105】

### Reference Example 4

A mixture of benzyl 3-benzyloxy-1-phenyl-1H-pyrazole-5-carboxylate (50.88 g), 1N aqueous sodium hydroxide solution



(200 ml), tetrahydrofuran (200 ml) and ethanol (200 ml) was refluxed at room temperature for 5 hours. 1N Hydrochloric acid (200 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-benzyloxy-1-phenyl-1H-pyrazole-5-carboxylic acid (36.91 g, yield 95%). The crystals were recrystallized from acetone-isopropyl ether. melting point: 163-164°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 5.27 (2H, s), 6.52 (1H, s), 7.30-7.50 (10H, m).

#### Reference Example 5

A mixture of 3-benzyloxy-1-phenyl-1H-pyrazole-5-carboxylic acid (33.00 g), iodomethane (8.5 ml), potassium carbonate (18.88 g) and N,N-dimethylformamide (300 ml) was stirred at room temperature overnight. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-benzyloxy-1-phenyl-1H-pyrazole-5-carboxylate (33.48 g, yield 97%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 53-54°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.77 (3H, s), 5.28 (2H, s), 6.44 (1H, s), 7.32-7.49 (10H, m).

#### Reference Example 6

A mixture of methyl 3-benzyloxy-1-phenyl-1H-pyrazole-5-carboxylate (15.00 g), 5% palladium-carbon (10.92 g) and tetrahydrofuran (200 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl

3-hydroxy-1-phenyl-1H-pyrazole-5-carboxylate (10.30 g, yield 97%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). The crystals were recrystallized from tetrahydrofuran-isopropyl ether.

5 melting point: 227-228°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.77 (3H, s), 6.32 (1H, s), 7.35-7.54 (5H, m), 10.77 (1H, br s).

【0106】

#### Reference Example 7

10 To a mixture of methyl 3-benzyloxy-1-phenyl-1H-pyrazole-5-carboxylate (14.53 g) and tetrahydrofuran (300 ml) was slowly added lithium aluminum hydride (1.79 g) at 0°C and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was slowly added sodium sulfate 10 hydrate  
15 (15.20 g) at 0°C and the mixture was stirred at room temperature for 30 minutes. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-1-phenyl-1H-pyrazol-5-yl)methanol (11.65 g, yield  
20 88%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 87-88°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.79 (1H, t, J=6.0 Hz), 4.61 (2H, d, J=6.0  
25 Hz), 5.28 (2H, s), 5.94 (1H, s), 7.30-7.60 (10H, m).

#### Reference Example 8

A mixture of (3-benzyloxy-1-phenyl-1H-pyrazol-5-yl)methanol (11.20 g), activated manganese dioxide (30.00 g) and tetrahydrofuran (300 ml), was stirred overnight at room  
30 temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-benzyloxy-1-phenyl-1H-pyrazole-5-carbaldehyde (10.10 g, yield 91%) was obtained as a pale-yellow oily substance from a fraction eluted with  
35 ethyl acetate-hexane (1:2, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 5.31 (2H, s), 6.51 (1H, s), 7.32-7.52 (10H, m), 9.78 (1H, s).

#### Reference Example 9

To a mixture of 3-benzyloxy-1-phenyl-1H-pyrazole-5-carbaldehyde (6.24 g), ethyl diethylphosphonoacetate (5.55 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 960 mg) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(3-benzyloxy-1-phenyl-1H-pyrazol-5-yl)propenoate (7.33 g, yield 94%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.30 (3H, t, J=6.8 Hz), 4.23 (2H, q, J=6.8 Hz), 5.29 (2H s), 6.18 (1H, s), 6.33 (1H, d, J=15.8 Hz), 7.28-7.55 (10H, m).

【0107】

#### Reference Example 10

A mixture of ethyl (E)-3-(3-benzyloxy-1-phenyl-1H-pyrazol-5-yl)propenoate (7.33 g), 5% palladium-carbon (7.11 g) and tetrahydrofuran (50 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (4.85 g, yield 89%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). The crystals were recrystallized from acetone-hexane. melting point: 150-151°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.23 (3H, t, J=7.2 Hz), 2.52-2.60 (2H, m), 2.86-2.94 (2H, m), 4.11 (2H, q, J=7.2 Hz), 5.59 (1H, s), 7.33-7.51 (5H, m).

### Reference Example 11

A mixture of methyl 3-hydroxy-1-methyl-1H-pyrazole-5-carboxylate (1.45 g), benzyl bromide (1.16 ml), potassium carbonate (1.54 g) and N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-benzyloxy-1-methyl-1H-pyrazole-5-carboxylate (2.20 g, yield 96%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.86 (3H, s), 4.05 (3H, s), 5.19 (2H, s), 6.21 (1H, s), 7.27-7.50 (5H, m).

### Reference Example 12

To a mixture of methyl 3-benzyloxy-1-methyl-1H-pyrazole-5-carboxylate (9.60 g) and tetrahydrofuran (100 ml) was slowly added lithium aluminum hydride (890 mg) at 0°C and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was slowly added sodium sulfate 10 hydrate (8.43 g) at 0°C, and the mixture was stirred at room temperature for 1 hour. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-1-methyl-1H-pyrazol-5-yl)methanol (8.52 g, quantitative) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.72 (1H, br s), 3.76 (3H, s), 4.58 (2H, d, J=6.2 Hz), 5.16 (2H, s), 5.64 (1H, s), 7.27-7.50 (5H, m).

【0108】

### Reference Example 13

A mixture of (3-benzyloxy-1-methyl-1H-pyrazol-5-yl)methanol (9.40 g), activated manganese dioxide (29.10 g) and tetrahydrofuran (200 ml) was stirred overnight at room

temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-benzyloxy-1-methyl-1H-pyrazole-5-carbaldehyde (6.05 g, yield 65%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 49.5-50.5°C.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 4.05 (3H, s), 5.22 (2H, s), 6.25 (1H, s), 7.26-7.51 (5H, m), 9.73 (1H, s).

#### 10 Reference Example 14

To a mixture of 3-benzyloxy-1-methyl-1H-pyrazole-5-carbaldehyde (3.05 g), ethyl diethylphosphonoacetate (3.25 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 575 mg) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(3-benzyloxy-1-methyl-1H-pyrazol-5-yl)propenoate (3.34 g, yield 83%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.33 (3H, t, J=7.0 Hz), 3.82 (3H, s), 4.26 (2H, q, J=7.0 Hz), 5.18 (2H, s), 5.95 (1H, s), 6.27 (1H, d, J=15.8 Hz), 7.27-7.53 (6H, m).

#### Reference Example 15

A mixture of ethyl (E)-3-(3-benzyloxy-1-methyl-1H-pyrazol-5-yl)propenoate (730 mg), 10% palladium-carbon (73 mg) and methanol (15 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The obtained colorless crystals were collected by filtration to give ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propionate (440 mg, yield 87%). The crystals were recrystallized from ethyl

acetate-hexane. melting point: 132-135°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.26 (3H, t, J=6.9 Hz), 2.59-2.66 (2H, m), 2.80-2.87 (2H, m), 3.61 (3H, s), 4.15 (2H, q, J=6.9 Hz), 5.39 (1H, s).

5      【0109】

#### Reference Example 16

A mixture of ethyl 3-methyl-1H-pyrazole-4-carboxylate (23.10 g), 2-chloro-5-(trifluoromethyl)pyridine (25.09 g), potassium carbonate (19.00 g) and N,N-dimethylformamide (300 ml) was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (40.22 g, yield 97%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 88-89°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.38 (3H, t, J=7.2 Hz), 2.57 (3H, s), 4.34 (2H, q, J=7.2 Hz), 8.05 (1H, dd, J=2.4, 9.3 Hz), 8.10 (1H, d, J=9.3 Hz), 8.64-8.72 (1H, m), 9.00 (1H, s).

#### Reference Example 17

To a solution of ethyl 3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (35.19 g) in tetrahydrofuran (300 ml) was dropwise added a 1.0 M solution (360 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (29.33

g, yield 97%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 157-158°C.

5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.46 (1H, t, J=5.4 Hz), 2.39 (3H, s), 4.64 (2H, d, J=5.4 Hz), 7.98-8.04 (2H, m), 8.49 (1H, s), 8.60-8.66 (1H, m).

#### Reference Example 18

To a mixture of N-hydroxy-4-  
10 (trifluoromethyl)benzenecarboximidoyl chloride (13.11 g), 5-hexyn-1-ol (5.88 g) and tetrahydrofuran (300 ml) was dropwise added a solution (50 ml) of triethylamine (17 ml) in tetrahydrofuran at 0°C, and the mixture was stirred at room temperature overnight. The reaction mixture was poured into  
15 dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol  
20 (13.92 g, yield 83%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 68-69°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.60-1.98 (4H, m), 2.80-2.95 (2H, m), 3.66-  
25 3.78 (2H, m), 6.36 (1H, s), 7.66-7.76 (2H, m), 7.86-7.96 (2H, m).

【0110】

#### Reference Example 19

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-  
30 isoxazolyl}-1-butanol (7.00 g), triethylamine (4 ml) and ethyl acetate (180 ml), was dropwise added a solution (20 ml) of methanesulfonyl chloride (2 ml) in ethyl acetate at 0°C, and the mixture was stirred at room temperature overnight. The reaction mixture was poured into dilute hydrochloric acid, and  
35 extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated aqueous sodium hydrogen carbonate and then saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butyl methanesulfonate (8.42 g, yield 95%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.78-2.04 (4H, m), 2.82-2.94 (2H, m), 3.14 (3H, s), 4.22-4.34 (2H, m), 6.36 (1H, s), 7.65-7.76 (2H, m), 7.86-7.97 (2H, m).

#### Reference Example 20

A mixture of ethyl 3-isopropyl-1H-pyrazole-4-carboxylate (5.00 g), 2-chloro-5-(trifluoromethyl)pyridine (4.95 g), potassium carbonate (3.80 g) and N,N-dimethylformamide (50 ml) was stirred overnight at  $100^\circ\text{C}$ . The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (8.61 g, yield 96%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point:  $94-95^\circ\text{C}$ .

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.32-1.44 (9H, m), 3.52-3.68 (1H, m), 4.33 (2H, q,  $J=7.0$  Hz), 8.03 (1H, dd,  $J=2.2, 8.8$  Hz), 8.14 (1H, d,  $J=8.8$  Hz), 8.68 (1H, d,  $J=2.2$  Hz), 8.98 (1H, s).

#### Reference Example 21

To a solution of ethyl 3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (8.50 g) in tetrahydrofuran (200 ml) was dropwise added a 1.0 M solution (60 ml) of diisobutylaluminum hydride in hexane at  $0^\circ\text{C}$ , and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid,



and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-isopropyl-1-[5-

5 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methanol (7.20 g, yield 97%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 119-120°C.

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.36 (6H, d, J=6.8 Hz), 1.45 (1H, t, J=5.6 Hz), 3.05-3.24 (1H, m), 4.67 (2H, d, J=5.6 Hz), 7.92-8.10 (2H, m), 8.49 (1H, s), 8.59-8.67 (1H, m).

【0111】

#### Reference Example 22

15 A mixture of 3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methanol (5.85 g), activated manganese dioxide (15.44 g) and tetrahydrofuran (300 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. 20 The residue was subjected to silica gel column chromatography, and 3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (5.22 g, yield 90%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl 25 acetate-hexane. melting point: 89-90°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.38 (6H, d, J=7.0 Hz), 3.42-3.59 (1H, m), 8.06 (1H, dd, J=2.2, 8.4 Hz), 8.15 (1H, d, J=8.4 Hz), 8.70 (1H, d, J=2.2 Hz), 9.04 (1H, s), 10.06 (1H, s).

#### Reference Example 23

30 To a mixture of 3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (5.00 g), ethyl diethylphosphonoacetate (4.05 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 730 mg) at 0°C and the mixture was stirred overnight at room temperature. The 35 reaction mixture was poured into water, and extracted with

ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl  
5 (E)-3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (5.93 g, yield 95%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 112-113°C.

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.34 (3H, t, J=7.4 Hz), 1.37 (6H, d, J=7.0 Hz), 3.14-3.32 (1H, m), 4.26 (2H, q, J=7.4 Hz), 6.29 (1H, d, J=16.0 Hz), 7.63 (1H, d, J=16.0 Hz), 7.96-8.15 (2H, m), 8.63-8.69 (1H, m), 8.75 (1H, s).

#### Reference Example 24

15 A mixture of ethyl (E)-3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (5.80 g), 5% palladium-carbon (1.35 g) and tetrahydrofuran (50 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the  
20 filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (5.82 g, quantitative) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.27 (3H, t, J=7.0 Hz), 1.33 (6H, d, J=7.0 Hz), 2.58-3.16 (6H, m), 4.16 (2H, q, J=7.0 Hz), 7.90-8.06 (2H, m), 8.26-8.33 (1H, m), 8.56-8.64 (1H, m).

【0112】

#### Reference Example 25

30 To a solution of ethyl 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (5.82 g) in tetrahydrofuran (50 ml) was dropwise added a 1.0 M solution (40 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour.

35 The reaction mixture was poured into dilute hydrochloric acid,

and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-isopropyl-1-[5-

5 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (4.50 g, yield 88%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 87-88°C.

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.33 (6H, d, J=7.0 Hz), 1.82-2.02 (2H, m), 2.53-2.68 (2H, m), 2.95-3.16 (1H, m), 3.68-3.84 (2H, m), 7.90-8.08 (2H, m), 8.28 (1H, s), 8.57-8.64 (1H, m).

#### Reference Example 26

To a solution of methyl 3-{3-isopropyl-1-[5-  
15 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1-methyl-1H-pyrazole-5-carboxylate (1.90 g) in tetrahydrofuran (30 ml) was dropwise added a 1.0 M solution (15 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction  
20 mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and (3-{3-isopropyl-1-[5-  
25 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1-methyl-1H-pyrazol-5-yl)methanol (1.70 g, yield 96%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.36 (6H, d, J=7.0 Hz), 3.04-3.27 (1H, m),  
30 3.78 (3H, s), 4.59 (2H, s), 5.13 (2H, s), 5.64 (1H, s), 7.97 (1H, dd, J=2.2, 8.8 Hz), 8.06 (1H, d, J=8.8 Hz), 8.56 (1H, s), 8.60-8.64 (1H, m).

#### Reference Example 27

A mixture of (3-{3-isopropyl-1-[5-(trifluoromethyl)-2-  
35 pyridyl]-1H-pyrazol-4-ylmethoxy}-1-methyl-1H-pyrazol-5-

yl)methanol (1.70 g), activated manganese dioxide (5.11 g) and tetrahydrofuran (50 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected  
5 to silica gel column chromatography, and 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1-methyl-1H-pyrazole-5-carbaldehyde (1.41 g, yield 83%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized  
10 from ethyl acetate-hexane. melting point: 112-113°C.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.37 (6H, d, J=6.8 Hz), 3.07-3.25 (1H, m), 4.06 (3H, s), 5.18 (2H, s), 6.25 (1H, s), 7.98 (1H, dd, J=2.2, 8.4 Hz), 8.07 (1H, d, J=8.4 Hz), 8.58 (1H, s), 8.60-8.65 (1H, m), 9.75 (1H, s).

15     **[0113]**

#### **Reference Example 28**

A mixture of ethyl 3-(3-ethoxy-1H-pyrazol-4-yl)propionate (12.98 g), 2-chloro-5-(trifluoromethyl)pyridine (11.10 g), potassium carbonate (12.33 g) and N,N-dimethylformamide (150  
20 ml) was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. To a solution of the residue in tetrahydrofuran  
25 (200 ml) was dropwise added a 1.0 M solution (140 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was  
30 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (6.10 g, yield 32%) was obtained as colorless crystals from a  
35 fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

The crystals were recrystallized from ethyl acetate-hexane.

melting point: 85-86°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.44 (3H, t, J=7.2 Hz), 1.65 (1H, br t), 1.80-1.94 (2H, m), 2.54 (2H, t, J=7.2 Hz), 3.64-3.78 (2H, m), 4.38  
5 (2H, q, J=7.2 Hz), 7.82 (1H, d, J=8.7 Hz), 7.91 (1H, dd, J=2.4, 8.7 Hz), 8.19 (1H, s), 8.53-8.59 (1H, m).

#### Reference Example 29

To a solution of methyl 1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-  
10 pyrazole-5-carboxylate (4.74 g) in tetrahydrofuran (30 ml) was dropwise added a 1.0 M solution (30 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate.  
15 The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and (1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazol-5-yl)methanol (4.18 g, yield  
20 88%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 128-129°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.58 (1H, t, J=5.7 Hz), 2.40 (3H, s), 3.77  
25 (3H, s), 4.59 (2H, d, J=5.7 Hz), 5.10 (2H, s), 5.63 (1H, s), 7.94-8.06 (2H, m), 8.56 (1H, s), 8.58-8.67 (1H, m).

#### Reference Example 30

A mixture of (1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-  
30 pyrazol-5-yl)methanol (4.00 g), activated manganese dioxide (12.18 g) and tetrahydrofuran (100 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 1-methyl-3-  
35 {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-

ylmethoxy)-1H-pyrazole-5-carbaldehyde (3.39 g, yield 85%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 130-  
5 131°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.41 (3H, s), 4.06 (3H, s), 5.16 (2H, s), 6.25 (1H, s), 7.93-8.08 (2H, m), 8.59 (1H, s), 8.60-8.67 (1H, m).

【0114】

#### Reference Example 31

10 A mixture of ethyl 3-propyl-1H-pyrazole-4-carboxylate (25.88 g), 2-chloro-5-(trifluoromethyl)pyridine (25.14 g), potassium carbonate (34.11 g) and N,N-dimethylformamide (300 ml) was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl  
15 acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (38.45 g, yield 85%) was  
20 obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from isopropyl ether-hexane. melting point: 102-103°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.03 (3H, t, J=7.2 Hz), 1.38 (3H, t, J=7.0  
25 Hz), 1.66-1.88 (2H, m), 2.86-3.00 (2H, m), 4.33 (2H, q, J=7.0 Hz), 7.99-8.16 (2H, m), 8.65-8.72 (1H, m), 8.99 (1H, s).

#### Reference Example 32

To a solution of ethyl 3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (36.41 g) in  
30 tetrahydrofuran (300 ml) was dropwise added a 1.0 M solution (250 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was  
35 washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and {3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (30.22 g, yield 95%) was obtained as colorless crystals from a fraction  
5 eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 120-121°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.03 (3H, t, J=7.4 Hz), 1.45 (1H, t, J=5.4 Hz), 1.65-1.88 (2H, m), 2.65-2.77 (2H, m), 4.64 (2H, d, J=5.4  
10 Hz), 7.93-8.08 (2H, m), 8.49 (1H, s), 8.61-8.66 (1H, m).

#### Reference Example 33

A mixture of {3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (10.00 g), activated manganese dioxide (29.48 g) and tetrahydrofuran (300 ml) was stirred  
15 overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (8.87 g, yield 89%) was obtained as colorless  
20 crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 52-53°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.03 (3H, t, J=7.2 Hz), 1.68-1.89 (2H, m), 2.88-3.02 (2H, m), 8.07 (1H, dd, J=2.2, 8.8 Hz), 8.14 (1H, d, J=8.8 Hz), 8.67-8.74 (1H, m), 9.04 (1H, s), 10.04 (1H, s).  
25

【0115】

#### Reference Example 34

To a mixture of 3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (8.70 g), ethyl  
30 diethylphosphonoacetate (8.25 g) and N,N-dimethylformamide (100 ml) was added sodium hydride (60%, in oil, 1.45 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute  
35 hydrochloric acid and then with saturated aqueous sodium

chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propenoate (10.14 g, yield 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 104-105°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.04 (3H, t, J=7.2 Hz), 1.34 (3H, t, J=7.0 Hz), 1.67-1.89 (2H, m), 2.78 (2H, t, J=7.6 Hz), 4.27 (2H, q, J=7.0 Hz), 6.27 (1H, d, J=16.2 Hz), 7.60 (1H, d, J=16.2 Hz), 7.97-8.11 (2H, m), 8.64-8.68 (1H, m), 8.75 (1H, s).

#### Reference Example 35

A mixture of ethyl (E)-3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propenoate (10.00 g), 5% palladium-carbon (3.03 g) and tetrahydrofuran (100 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propionate (9.36 g, 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 73-74°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (3H, t, J=7.4 Hz), 1.26 (3H, t, J=7.0 Hz), 1.62-1.86 (2H, m), 2.56-2.68 (4H, m), 2.75-2.86 (2H, m), 4.16 (2H, q, J=7.0 Hz), 7.91-8.04 (2H, m), 8.30 (1H, s), 8.58-8.64 (1H, m).

#### Reference Example 36

To a solution of ethyl 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propionate (9.10 g) in tetrahydrofuran (100 ml) was dropwise added a 1.0 M solution (60 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid,



and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-propyl-1-[5-

5 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (7.61 g, yield 95%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 96-97°C.

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (3H, t, J=7.2 Hz), 1.32 (1H, br t), 1.64-1.99 (4H, m), 2.50-2.68 (4H, m), 3.68-3.80 (2H, m), 7.91-8.05 (2H, m), 8.29 (1H, s), 8.58-8.63 (1H, m).

【0116】

#### Reference Example 37

15 A mixture of ethyl 3-hydroxy-1-methyl-1H-pyrazole-4-carboxylate (25.50 g), benzyl bromide (17.8 ml), potassium carbonate (31.10 g) and N,N-dimethylformamide (250 ml) was stirred overnight at 50°C. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl  
20 acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-benzyloxy-1-methyl-1H-pyrazole-4-carboxylate (31.90 g, yield 82%) was obtained as  
25 colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 66-67°C.

#### Reference Example 38

To a solution of ethyl 3-benzyloxy-1-methyl-1H-pyrazole-  
30 4-carboxylate (18.00 g) in tetrahydrofuran (200 ml) was added lithium aluminum hydride (2.62 g) at 0°C, and the mixture was stirred at room temperature for 1 hour. Sodium sulfate 10 hydrate (22.20 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The  
35 precipitate was filtered off and the filtrate was concentrated.

The residue was subjected to silica gel column chromatography, and (3-benzyloxy-1-methyl-1H-pyrazol-4-yl)methanol (23.90 g, yield 91%) was obtained as a colorless oil from a fraction eluted with ethyl acetate.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.74 (1H, t,  $J=5.4$  Hz), 3.72 (3H, s), 4.47 (2H, d,  $J=5.4$  Hz), 5.24 (2H, s), 7.17 (1H, s), 7.28-7.47 (5H, m).

#### Reference Example 39

A mixture of (3-benzyloxy-1-methyl-1H-pyrazol-4-yl)methanol (18.40 g), activated manganese dioxide (40.00 g) and tetrahydrofuran (200 ml) was stirred at room temperature for 9 hours. Manganese dioxide was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-benzyloxy-1-methyl-1H-pyrazole-4-carbaldehyde (14.80 g, yield 81%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (2:1, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.78 (3H, s), 5.32 (2H, s), 7.29-7.50 (5H, m), 7.69 (1H, s), 9.76 (1H, s).

20 **[0117]**

#### Reference Example 40

To a mixture of potassium t-butoxide (2.24 g) and dimethoxyethane (10 ml) was added a solution of p-toluenesulfonylmethyl isocyanide (2.05 g) in dimethoxyethane (10 ml) at  $-78^\circ\text{C}$  and the mixture was stirred for 5 minutes. Then a solution of 3-benzyloxy-1-methyl-1H-pyrazole-4-carbaldehyde (2.16 g) in dimethoxyethane (10 ml) was added. After stirring at the same temperature for 1 hour, the mixture was stirred for 1 hour while raising the temperature to room temperature. To the obtained mixture was added methanol (380 ml), and mixture was refluxed for 1 hour. After cooling, the reaction mixture was poured into saturated aqueous ammonium chloride solution, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue

was subjected to silica gel column chromatography, and (3-benzyloxy-1-methyl-1H-pyrazol-4-yl)acetonitrile (1.86 g, yield 82%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.43 (2H, s), 3.74 (3H, s), 5.22 (2H, s), 7.21 (1H, s), 7.29-7.47 (5H, m).

#### Reference Example 41

A mixture of (3-benzyloxy-1-methyl-1H-pyrazol-4-yl)acetonitrile (12.0 g), 4N aqueous sodium hydroxide solution  
10 (100 ml), tetrahydrofuran (100 ml) and ethanol (100 ml) was refluxed for 21 hours. After cooling, the mixture was neutralized with dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and  
15 concentrated. A mixture of the residue, methyl iodide (4.95 ml), potassium carbonate (14.7 g) and N,N-dimethylformamide (100 ml) was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with  
20 saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-benzyloxy-1-methyl-1H-pyrazol-4-yl)acetate (12.2 g, yield 88%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane  
25 (1:1, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.41 (2H, s), 3.68 (3H, s), 3.73 (3H, s), 5.22 (2H, s), 7.19 (1H, s), 7.30-7.46 (5H, m).

#### Reference Example 42

A mixture of methyl (3-benzyloxy-1-methyl-1H-pyrazol-4-yl)acetate (12.2 g), 5% palladium-carbon (25.0 g),  
30 tetrahydrofuran (100 ml) and ethanol (100 ml) was stirred under a hydrogen atmosphere for 5 hours. Palladium-carbon was removed by filtration and the filtrate was concentrated to give methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (6.33  
35 g, yield 79%) as colorless crystals. The crystals were

recrystallized from tetrahydrofuran-hexane. melting point: 118-119°C.

【0118】

#### Reference Example 43

5 A mixture of ethyl 3-hydroxy-1-phenyl-1H-pyrazole-4-carboxylate (7.76 g), benzyl bromide (3.97 ml), potassium carbonate (6.91 g) and N,N-dimethylformamide (75 ml) was stirred overnight at 50°C. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl  
10 acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-benzyloxy-1-phenyl-1H-pyrazole-4-carboxylate (8.29 g, yield 77%) was obtained as  
15 colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 113-114°C.

#### Reference Example 44

To a solution of ethyl 3-benzyloxy-1-phenyl-1H-pyrazole-  
20 4-carboxylate (8.06 g) in tetrahydrofuran (100 ml) was added lithium aluminum hydride (0.95 g) at 0°C, and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added sodium sulfate 10 hydrate (8.06 g), and the mixture was stirred at room temperature for 1 hour. The  
25 precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-1-phenyl-1H-pyrazol-4-yl)methanol (5.91 g, yield 84%) was obtained as colorless crystals from a fraction eluted with ethyl acetate. The  
30 crystals were recrystallized from ethyl acetate-hexane. melting point: 93-94°C.

#### Reference Example 45

A mixture of (3-benzyloxy-1-phenyl-1H-pyrazol-4-yl)methanol (5.61 g), activated manganese dioxide (15.00 g)  
35 and tetrahydrofuran (75 ml) was stirred overnight at room

temperature. Manganese dioxide was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-benzyloxy-1-phenyl-1H-pyrazole-4-carbaldehyde (5.03 g, yield 90%) was obtained as  
5 colorless crystals from a fraction eluted with ethyl acetate-hexane (2:1, volume ratio). The crystals were recrystallized from tetrahydrofuran-hexane. melting point: 153-154°C.

【0119】

#### Reference Example 46

10 To a mixture of potassium t-butoxide (3.82 g) and dimethoxyethane (20 ml) was added a solution of p-toluenesulfonylmethyl isocyanide (3.51 g) in dimethoxyethane (20 ml) at -78°C, and the mixture was stirred for 5 minutes. Then a solution of 3-benzyloxy-1-phenyl-1H-pyrazole-4-  
15 carbaldehyde (4.73 g) in dimethoxyethane (80 ml) was added. After stirring at the same temperature for 1 hour, the mixture was stirred for 1 hour while raising the temperature to room temperature. Methanol (100 ml) was added to the obtained mixture, and the mixture was refluxed for 1 hour. After  
20 cooling, the reaction mixture was poured into saturated aqueous ammonium chloride solution, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column  
25 chromatography, and (3-benzyloxy-1-phenyl-1H-pyrazol-4-yl)acetonitrile (3.31 g, yield 67%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). The crystals were recrystallized from tetrahydrofuran-hexane. melting point: 102-103°C.

#### 30 Reference Example 47

A mixture of (3-benzyloxy-1-phenyl-1H-pyrazol-4-yl)acetonitrile (3.01 g), 6N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was  
35 refluxed for 3 days. After cooling, the mixture was neutralized with dilute hydrochloric acid, and extracted with

ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated to give (3-benzyloxy-1-phenyl-1H-pyrazol-4-yl)acetic acid (2.63 g, yield 82%) as colorless crystals. The  
5 crystals were recrystallized from acetone-hexane. melting point: 105-106°C.

#### Reference Example 48

A mixture of (3-benzyloxy-1-phenyl-1H-pyrazol-4-yl)acetic acid (2.47 g), methyl iodide (0.75 ml), potassium carbonate  
10 (2.21 g) and N,N-dimethylformamide (25 ml) was stirred at room temperature for 1 hour. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was  
15 subjected to silica gel column chromatography, and methyl (3-benzyloxy-1-phenyl-1H-pyrazol-4-yl)acetate (2.55 g, yield 99%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 74-  
20 75°C.

【0120】

#### Reference Example 49

A mixture of methyl (3-benzyloxy-1-phenyl-1H-pyrazol-4-yl)acetate (2.35 g), 5% palladium-carbon (4.00 g),  
25 tetrahydrofuran (25 ml) and methanol (25 ml) was stirred for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated to give methyl (3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acetate (1.58 g, yield 93%) as colorless crystals. The crystals were recrystallized  
30 from ethyl acetate-hexane. melting point: 144-145°C.

#### Reference Example 50

A mixture of [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide (18.86 g), sodium  
hydride (60%, in oil, 1.70 g) and N,N-dimethylformamide (100  
35 ml) was stirred at room temperature for 30 minutes. 3-Propyl-

1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (9.00 g) was added thereto and the mixture was stirred at 70°C for 5 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the residue, 5% palladium-carbon (2.04 g) and tetrahydrofuran (100 ml) was stirred for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The obtained residue was dissolved in tetrahydrofuran (150 ml), and 1N hydrochloric acid (200 ml) and methanol (50 ml) were added, which was followed by stirring at room temperature for 2 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography and 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}butanal (8.08 g, yield 78%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 71-72°C.

#### Reference Example 51

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}butanal (7.85 g), methanol (20 ml) and tetrahydrofuran (20 ml) was slowly added sodium borohydride (700 mg) at 0°C, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated to give 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-butanol (7.48 g, yield 95%) as colorless crystals. The crystals were recrystallized from ethyl acetate-hexane. melting point: 80-81°C.

【0121】

#### Reference Example 52

To a mixture of 2-(1,3-dioxolan-2-yl)ethyltetraphenylphosphonium bromide (18.95 g) and N,N-dimethylformamide (178 ml) was added sodium hydride (60%, in oil, 1.71 g) at 0°C and the mixture was stirred at room temperature for 30 minutes. Then, 3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazole-4-carbaldehyde (10.09 g) was added and the mixture was stirred at room temperature overnight, and at 70°C for 4 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:15, volume ratio). A mixture of the obtained oily substance, 5% palladium-carbon (1.28 g) and ethanol (174 ml) was stirred at room temperature for 3.5 hours under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated to give 2-{4-[3-(1,3-dioxolan-2-yl)propyl]-3-isopropyl-1H-pyrazol-1-yl}-5-(trifluoromethyl)-pyridine (12.84 g, yield 98%) as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.32 (6H, d, J = 7.0 Hz), 1.72 - 1.82 (4H, m), 2.46 - 2.58 (2H, m), 2.92 - 3.10 (1H, m), 3.82 - 4.00 (4H, m), 4.88 - 4.96 (1H, m), 7.88 - 7.98 (1H, m), 8.02 (1H, d, J = 8.4 Hz), 8.27 (1H, s), 8.56 - 8.61 (1H, m).

#### Reference Example 53

A mixture of 2-{4-[3-(1,3-dioxolan-2-yl)propyl]-3-isopropyl-1H-pyrazol-1-yl}-5-(trifluoromethyl)-pyridine (12.84 g), 1N hydrochloric acid (100 ml), tetrahydrofuran (100 ml) and methanol (100 ml) was stirred overnight at 50°C. The reaction mixture was concentrated under reduced pressure, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried



(MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyraldehyde (11.25 g, yield 99%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.32 (6H, d, J = 6.9 Hz), 1.90 - 2.06 (2H, m), 2.44 - 2.60 (4H, m), 2.94 - 3.07 (1H, m), 7.90 - 7.98 (1H, m), 8.02 (1H, d, J = 8.7 Hz), 8.27 (1H, s), 8.55 - 8.61 (1H, m), 9.78 - 9.81 (1H, m).

#### 10 **Reference Example 54**

To a solution of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyraldehyde (11.25 g) in ethanol (170 ml) was added sodium borohydride (1.57 g) at room temperature and the mixture was stirred for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (6.11 g, yield 54%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). Along therewith, 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyraldehyde (2.46 g), which was a starting material, was also recovered. The obtained colorless crystals were recrystallized from ethyl acetate-hexane. melting point: 67-68°C.

**[0122]**

#### **Reference Example 55**

30 A mixture of ethyl (3-ethoxy-1H-pyrazol-4-yl)acetate (18.95 g), sodium hydride (60%, in oil, 4.59 g) and N,N-dimethylformamide (478 ml) was stirred at room temperature for 1 hour, to which 2-chloro-5-(trifluoromethyl)pyridine (20.82 g) was added and the mixture was stirred overnight. The reaction mixture was poured into water, and extracted with

ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl {3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}acetate (11.27 g, yield 41%) was  
5 obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.29 (3H, t,  $J = 7.4$  Hz), 1.42 (3H, t,  $J = 7.0$  Hz), 3.46 (2H, s), 4.20 (2H, q,  $J = 7.4$  Hz), 4.36 (2H, q,  $J =$   
10 7.0 Hz), 7.83 (1H, d,  $J = 8.8$  Hz), 7.84 - 7.96 (1H, m), 8.39 (1H, s), 8.54 - 8.60 (1H, m).

#### Reference Example 56

To a solution of ethyl {3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}acetate (11.27 g) in  
15 tetrahydrofuran (400 ml) was dropwise added a 1.0 M solution (117 ml) of diisobutylaluminum hydride in hexane at  $0^\circ\text{C}$ , and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was  
20 washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (4.38 g, yield 45%) was obtained as pale-yellow crystals from a  
25 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point:  $75-76^\circ\text{C}$ .

#### Reference Example 57

To a solution of ethyl 3-(3-hydroxy-1H-pyrazol-4-yl)propanoate (7.40 g) in tetrahydrofuran (100 ml) were added  
30 di-tert-butyl dicarbonate (9.71 ml) and triethylamine (5.89 ml) at room temperature and the mixture was stirred overnight. The reaction mixture was concentrated to give a residue. To a mixture of the obtained residue, benzyl alcohol (5.00 ml),  
35 tributylphosphine (20.1 ml) and tetrahydrofuran (805 ml) was

added a 40% toluene solution (52.9 ml) of 1,1'-diethyl azodicarboxylate at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography,  
5 and tert-butyl 3-benzyloxy-4-(2-ethoxycarbonylethyl)-1H-pyrazole-1-carboxylate (5.08 g, yield 34%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.23 (3H, t, J = 6.9 Hz), 1.61 (9H, s), 2.53 -  
10 2.60 (2H, m), 2.66 - 2.73 (2H, m), 5.34 (2H, s), 7.27 - 7.46 (5H, m), 7.65 (1H, s).

【0123】

#### Reference Example 58

To a solution of tert-butyl 3-benzyloxy-4-(2-  
15 ethoxycarbonylethyl)-1H-pyrazole-1-carboxylate (5.08 g) in ethyl acetate (13.6 ml) was added 4N ethyl acetate solution (43.6 ml) of hydrochloric acid and the mixture was stirred overnight. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution and extracted with  
20 ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated to give ethyl 3-(3-benzyloxy-1H-pyrazol-4-yl)propanoate (3.92 g, quantitative) as a colorless oil.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.22 (3H, t, J = 7.2 Hz), 2.04 - 2.59 (2H, m),  
25 2.69 - 2.75 (2H, m), 4.10 (2H, q, J = 7.2 Hz), 5.25 (2H, s), 7.19 (1H, s), 7.25 - 7.45 (5H, m).

#### Reference Example 59

A mixture of ethyl 3-(3-benzyloxy-1H-pyrazol-4-yl)propanoate (2.84 g), sodium hydride (60%, in oil, 497 mg)  
30 and N,N-dimethylformamide (104 ml) was stirred at room temperature for 1 hour and 2-chloro-5-(trifluoromethyl)pyridine (2.26 g) was added. The mixture was stirred overnight. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was  
35 washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propanoate (3.14 g, yield 72%) was obtained as a colorless oil from a  
5 fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.24 (3H, t, J = 7.2 Hz), 2.57 - 2.65 (2H, m), 2.74 - 2.81 (2H, m), 4.12 (2H, q, J = 7.2 Hz), 5.35 (2H, s), 7.39 - 7.43 (3H, m), 7.44 - 7.50 (2H, m), 7.82 (1H, d, J = 8.4 Hz), 7.89 - 7.94 (1H, m), 8.22 (1H, s), 8.53 - 8.57 (1H, m).

10 **Reference Example 60**

To a solution of ethyl 3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propanoate (3.14 g) in tetrahydrofuran (75 ml) was dropwise added a 1.0 M solution (16.5 ml) of diisobutylaluminum hydride in hexane at  
15 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue  
20 was subjected to silica gel column chromatography, and 3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (2.41 g, yield 85%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from  
25 ethyl acetate-hexane. melting point: 79-81°C.

[0124]

**Reference Example 61**

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (1.20 g), triethylamine  
30 (613 μL) and tetrahydrofuran (37 ml) was added methanesulfonyl chloride (341 μL) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-  
35 pyrazol-4-yl}butyl methanesulfonate (1.25 g, yield 84%) was

obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 87-89°C.

5 **Reference Example 62**

To a mixture of 5-benzyloxy-2-methoxybenzaldehyde (3.45 g), ethyl diethylphosphonoacetate (3.41 ml) and N,N-dimethylformamide (100 ml) was added sodium hydride (60%, in oil, 684 mg) at 0°C and the mixture was stirred at room  
10 temperature for 2 days. The reaction mixture was poured into 0.1N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a pale-  
15 yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 5% palladium-carbon (1.00 g) and ethanol (150 ml) was stirred at room temperature for 2 hours under a hydrogen atmosphere. Palladium-carbon was removed by  
20 filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(5-hydroxy-2-methoxyphenyl)propanoate (2.54 g, yield 80%) was obtained as a brown oily substance from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio).  
25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.24 (3H, t, J = 6.8 Hz), 2.52 - 2.64 (2H, m), 2.82 - 2.94 (2H, m), 3.77 (3H, s), 4.12 (2H, q, J = 6.8 Hz), 4.94 (1H, brs), 6.61 - 6.74 (3H, m).

【0125】

**Reference Example 63**

30 To a mixture of ethyl 3-(3-phenyl-1H-pyrazol-4-yl)propionate (3.00 g), 2-chloro-5-(trifluoromethyl)pyridine (2.35 g) and N,N-dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 620 mg) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture  
35 was poured into water, and extracted with ethyl acetate. The

ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
5 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). To a solution of the obtained colorless oil in tetrahydrofuran (50 ml) was dropwise added a 1.0 M solution (30 ml) of diisobutylaluminum hydride in hexane at  $0^\circ\text{C}$ , and the mixture was stirred at room temperature for 1  
10 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-  
15 phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (3.85 g, yield 86%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point:  $99-100^\circ\text{C}$ .

20 **Reference Example 64**

A mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (10.05 g), activated manganese dioxide (31.48 g) and tetrahydrofuran (200 ml) was stirred overnight at room temperature. The insoluble material was  
25 removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (8.94 g, yield 90%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane  
30 (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point:  $226-227^\circ\text{C}$ .

**Reference Example 65**

To a mixture of 3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (8.30 g), ethyl  
35 diethylphosphonoacetate (8.50 g) and N,N-dimethylformamide (75

ml) was added sodium hydride (60%, in oil, 1.50 g) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute  
5 hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propenoate (9.53 g, yield 90%) was obtained as colorless  
10 crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 131-132°C.

[0126]

#### Reference Example 66

15 A mixture of ethyl (E)-3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propenoate (9.00 g), 5% palladium-carbon (2.42 g) and tetrahydrofuran (100 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the  
20 filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propionate (8.45 g, yield 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).  
25 The crystals were recrystallized from ethyl acetate-hexane. melting point: 50-51°C.

#### Reference Example 67

To a solution of ethyl 3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propionate (7.00  
30 g) in tetrahydrofuran (100 ml) was dropwise added a 1.0 M solution (50 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate  
35 layer was washed with saturated aqueous sodium chloride

solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and 3-(3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (5.63 g, yield 92%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 103-104°C.

#### Reference Example 68

To a solution of 2-benzyloxy-3-methoxybenzaldehyde (9.90 g) in tetrahydrofuran (100 ml) was added lithium aluminum hydride (1.15 g) at 0°C, and the mixture was stirred at room temperature for 1 hour. Sodium sulfate 10 hydrate (11.03 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 2-benzyloxy-3-methoxybenzyl alcohol (9.94 g, quantitative) was obtained as a colorless oil from a fraction eluted with ethyl acetate.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.97 (1H, t,  $J=6.6$  Hz), 3.91 (3H, s), 4.55 (2H, d,  $J=6.6$  Hz), 5.09 (2H, s), 6.86-6.96 (2H, m), 7.01-7.12 (1H, m), 7.28-7.49 (5H, m).

【0127】

#### Reference Example 69

To a mixture of 2-benzyloxy-3-methoxybenzyl alcohol (9.90 g), acetone cyanohydrin (4.60 g), triphenylphosphine (16.21 g) and tetrahydrofuran (200 ml) was dropwise added a 40% toluene solution (26.49 g) of diethyl azodicarboxylate at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and (2-benzyloxy-3-methoxyphenyl)acetonitrile (8.62 g, yield 84%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.53 (2H, s), 3.92 (3H, s), 5.09 (2H, s),



6.90-7.14 (3H, m), 7.32-7.46 (5H, m).

#### Reference Example 70

A mixture of (2-benzyloxy-3-methoxyphenyl)acetonitrile (8.62 g), 8N aqueous sodium hydroxide solution (40 ml) and  
5 ethanol (200 ml) was stirred under reflux overnight. After cooling, the reaction mixture was acidified by slowly adding conc. hydrochloric acid (30 ml). After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium  
10 chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. A mixture of the residue, a 10% solution (200 ml) of hydrochloric acid in methanol and methanol (200 ml) was stirred overnight at room temperature. After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate  
15 solution was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-benzyloxy-3-methoxyphenyl)acetate (7.40 g, yield 76%) was obtained as a colorless oil from a fraction eluted with ethyl  
20 acetate-hexane (1:4, volume ratio).  
 $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.61 (5H, s), 3.89 (3H, s), 5.03 (2H, s), 6.79-7.10 (3H, m), 7.25-7.56 (5H, m).

#### Reference Example 71

A mixture of methyl (2-benzyloxy-3-methoxyphenyl)acetate  
25 (7.40 g), 5% palladium-carbon (1.39 g) and tetrahydrofuran (100 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and was  
30 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio) to give methyl (2-hydroxy-3-methoxyphenyl)acetate (5.01 g, yield 99%) as a colorless oil.  
 $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.68 (2H, s), 3.70 (3H, s), 3.88 (3H, s), 5.88 (1H, s), 6.76-6.86 (3H, m).

35     **[0128]**

## Reference Example 72

A mixture of methyl 3,5-dihydroxybenzoate (500 mg), benzyl bromide (17.7 ml), potassium carbonate (20.62 g) and N,N-dimethylformamide (250 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained colorless crystals, methyl iodide (4.6 ml), potassium carbonate (7.90 g) and N,N-dimethylformamide (150 ml) was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with diethyl ether. The diethyl ether layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated to give methyl 3-benzyloxy-5-methoxybenzoate (15.54 g, yield 38%) as a pale-yellow oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) $\delta$ : 3.82 (3H, s), 3.91 (3H, s), 5.08 (2H, s), 6.73 (1H, t, J=2.3 Hz), 7.19-7.46 (7H, m).

## Reference Example 73

To a mixture of lithium aluminum hydride (5.40 g) and tetrahydrofuran (100 ml) was slowly added a solution of methyl 3-benzyloxy-5-methoxybenzoate (15.54 g) in tetrahydrofuran (20 ml) at 0°C, and the mixture was stirred at room temperature for 30 minutes. Acetone (80 ml) was slowly added to decompose excess lithium aluminum hydride, and brine (15.4 ml) was added. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-5-methoxyphenyl)methanol (14.00 g, quantitative) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) $\delta$ : 1.69 (1H, t, J=6.1Hz), 3.79 (3H, s), 4.63 (2H,

d, J=6.1Hz), 5.05 (2H, s), 6.47 (1H, t, J=2.3 Hz), 6.53-6.55 (1H, m), 6.66-6.68 (1H, m), 7.29-7.45 (5H, m).

#### Reference Example 74

A mixture of (3-benzyloxy-5-methoxyphenyl)methanol (6.03 g), activated manganese dioxide (18.0 g) and tetrahydrofuran (80 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). To a mixture of the obtained oil, ethyl diethylphosphonoacetate (4.84 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 950 mg) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(3-benzyloxy-5-methoxyphenyl)propenoate (3.96 g, yield 51%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.34 (3H, t, J=7.1 Hz), 3.80 (3H, s), 4.26 (2H, q, J=7.1 Hz), 5.06 (2H, s), 6.39 (1H, d, J=15.9 Hz), 6.57 (1H, t, J=2.2 Hz), 6.68 (1H, t, J=1.7 Hz), 6.75 (1H, t, J=1.7 Hz), 7.30-7.45 (5H, m), 7.59 (1H, d, J=15.9 Hz).

【0129】

#### Reference Example 75

A mixture of ethyl (E)-3-(3-benzyloxy-5-methoxyphenyl)propenoate (3.96 g), 5% palladium-carbon (0.4 g) and ethanol (25 ml) was stirred at room temperature overnight under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(3-hydroxy-5-methoxyphenyl)propionate (2.78 g, yield 98%) was

obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.25 (3H, t,  $J=7.1$  Hz), 2.60 (2H, t,  $J=7.8$  Hz), 2.86 (2H, t,  $J=7.8$  Hz), 3.76 (3H, s), 4.14 (2H, q,  $J=7.1$  Hz), 5.22 (1H, s), 6.25-6.35 (3H, m).

#### Reference Example 76

To a mixture of (3-benzyloxy-5-methoxyphenyl)methanol (8.00 g), acetone cyanohydrin (4.65 ml), tributylphosphine (13.3 g) and tetrahydrofuran (200 ml) was added 1,1'-azodicarbonyldipiperidine (16.53 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-5-methoxyphenyl)acetonitrile (5.77 g, yield 70%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.68 (2H, s), 3.78 (2H, s), 5.05 (2H, s), 6.46-6.56 (3H, m), 7.30-7.45 (5H, m).

#### Reference Example 77

A mixture of (3-benzyloxy-5-methoxyphenyl)acetonitrile (5.77 g), potassium hydroxide (4.50 g) and ethylene glycol (50 ml) was stirred overnight  $120^\circ\text{C}$ . The reaction mixture was poured into water, and washed with diethyl ether. The aqueous layer was acidified by adding hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated to give a residue. A mixture of the obtained residue, methyl iodide (1.80 ml), potassium carbonate (4.00 g) and  $\text{N,N}$ -dimethylformamide (50 ml), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-benzyloxy-5-methoxyphenyl)acetate (4.43 g, yield 68%) was

obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.56 (2H, s), 3.69 (3H, s), 3.77 (2H, s), 5.03 (2H, s), 6.44-6.47 (2H, m), 6.51-6.54 (1H, m), 7.29-7.45 (5H, m).

5  
[0130]

#### Reference Example 78

A mixture of methyl (3-benzyloxy-5-methoxyphenyl)acetate (4.43 g), 5% palladium-carbon (0.44 g) and ethanol (25 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-hydroxy-5-methoxyphenyl)acetate (2.97 g, yield 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.54 (2H, s), 3.70 (3H, s), 3.76 (2H, s), 5.38 (1H, br s), 6.32 (1H, t, J=2.3 Hz), 6.35-6.42 (2H, m).

#### Reference Example 79

20 A mixture of (p-hydroxyphenyl)acetonitrile (15.0 g), benzyl bromide (13.6 ml), potassium carbonate (15.6 g) and N,N-dimethylformamide (100 ml) was stirred overnight at room temperature. The reaction mixture was poured into water, The precipitated crystals were collected by filtration, washed well with water and dried to give (4-benzyloxyphenyl)acetonitrile (24.12 g, yield 96%). melting point: 70-71°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.68 (2H, s), 5.07 (2H, s), 6.95-6.99 (2H, m), 7.21-7.25 (2H, m), 7.30-7.45 (5H, m).

#### 30 Reference Example 80

To a mixture of (4-benzyloxyphenyl)acetonitrile (600 mg), methyl iodide (20.0 ml) and dimethyl sulfoxide (200 ml) was slowly added 50% aqueous sodium hydroxide solution at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water, and the precipitated

crystals were collected by filtration, washed well with water and dried to give 2-(4-benzyloxyphenyl)-2-methylpropanenitrile (25.88 g, yield 99%). melting point: 63-64°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.70 (6H, s), 5.07 (2H, s), 6.95-7.00 (2H, m),  
5 7.30-7.45 (7H, m).

【0131】

#### Reference Example 81

A mixture of 2-(4-benzyloxyphenyl)-2-methylpropanenitrile (25.88 g), potassium hydroxide (20.34 g) and ethylene glycol  
10 (200 ml) was stirred at 120°C for 2 days. The reaction mixture was poured into ice water, acidified by adding hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained  
15 colorless crystals were collected by filtration to give 2-(4-benzyloxyphenyl)-2-methylpropanoic acid (27.62 g, yield 99%). melting point: 128-130°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.58 (6H, s), 5.05 (2H, s), 6.92-6.97 (2H, m),  
7.29-7.45 (7H, m).

#### 20 Reference Example 82

A mixture of 2-(4-benzyloxyphenyl)-2-methylpropanoic acid (27.62 g), sulfuric acid (6 ml) and ethanol (500 ml) was refluxed for 14 hours. The reaction mixture was poured into ice water, and the precipitated crystals were collected by  
25 filtration, washed well with aqueous sodium hydrogen carbonate and water and dried to give ethyl 2-(4-benzyloxyphenyl)-2-methylpropanoate (28.20 g, yield 92%). melting point: 54-55°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.82 (3H, t, J=7.1 Hz), 1.55 (6H, s), 4.11  
(2H, q, J=7.1 Hz), 5.04 (2H, s), 6.90-6.95 (2H, m), 7.24-7.45  
30 (7H, m).

#### Reference Example 83

A mixture of ethyl 2-(4-benzyloxyphenyl)-2-methylpropanoate (28.20 g), 5% palladium-carbon (2.8 g) and ethanol (100 ml) was stirred overnight at room temperature  
35 under a hydrogen atmosphere. Palladium-carbon was removed by

filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 2-(4-hydroxyphenyl)-2-methylpropanoate (17.20 g, yield 87%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.19 (3H, t,  $J=7.1$  Hz), 1.55 (6H, s), 4.12 (2H, q,  $J=7.2$  Hz), 5.26 (1H, s), 6.74-6.79 (2H, m), 7.18-7.23 (2H, m)

【0132】

#### 10 Reference Example 84

To a mixture of (3-benzyloxyphenyl)methanol (22.09 g) and dichloroethane (250 ml) was added thionyl chloride (14.8 ml) at  $0^\circ\text{C}$ , and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated, and the residue was poured into aqueous sodium hydrogen carbonate and extracted with diethyl ether. The diethyl ether layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated to give a residue. A mixture of the obtained residue, sodium cyanide (5.32 g) and  $\text{N,N}$ -dimethylformamide (100 ml) was stirred overnight at  $50^\circ\text{C}$ . The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxyphenyl)acetonitrile (19.64 g, yield 85%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.72 (2H, s), 5.07 (2H, s), 6.89-6.96 (3H, m), 7.24-7.45 (6H, m).

#### 30 Reference Example 85

To a mixture of (3-benzyloxyphenyl)acetonitrile (19.64 g), methyl iodide (16.5 ml) and dimethyl sulfoxide (200 ml) was slowly added 50% aqueous sodium hydroxide solution (28.2 g) at  $0^\circ\text{C}$ , and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water, and

extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated to give 2-(3-benzyloxyphenyl)-2-methylpropanenitrile (21.63 g, yield 98%) as a yellow oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.71 (6H, s), 5.08 (2H, s), 6.90-6.94 (1H, m), 7.05-7.11 (2H, m), 7.28-7.47 (6H, m).

#### Reference Example 86

A mixture of 2-(3-benzyloxyphenyl)-2-methylpropanenitrile (21.63 g), potassium hydroxide (17.0 g) and ethylene glycol (150 ml) was stirred at 120°C for 2 days. The reaction mixture was poured into ice water, acidified by adding hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated to give 2-(3-benzyloxyphenyl)-2-methylpropanoic acid (20.68 g, yield 89%) as yellow crystals. melting point: 114-116°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.58 (6H, s), 5.05 (2H, s), 6.85-6.89 (2H, m), 6.98-7.05 (2H, m), 7.23-7.46 (6H, m).

[0133]

#### Reference Example 87

A mixture of 2-(3-benzyloxyphenyl)-2-methylpropanoic acid (20.68 g), potassium carbonate (10.6 g), methyl iodide (7.1 ml) and N,N-dimethylformamide (160 ml) was stirred at room temperature for 2 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 2-(3-benzyloxyphenyl)-2-methylpropanoate (19.62 g, yield 90%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.56 (6H, s), 3.63 (3H, s), 5.05 (2H, s), 6.84-6.97 (3H, m), 7.22-7.46 (6H, m)

#### Reference Example 88



A mixture of methyl 2-(3-benzyloxyphenyl)-2-methylpropanoate (19.62 g), 5% palladium-carbon (2.0 g) and ethanol (100 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by  
5 filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 2-(3-hydroxyphenyl)-2-methylpropanoate (12.32 g, yield 92%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio).  
10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.56 (6H, s), 3.66 (3H, s), 5.35 (1H, s), 6.72 (1H, ddd, J=8.1, 2.4, 1.0 Hz), 6.83 (1H, t, J=2.1 Hz), 6.89 (1H, ddd, J=7.8, 1.7, 1.0 Hz), 7.19 (1H, t, J=7.9 Hz)

#### Reference Example 89

A mixture of 3,4-dihydroxybenzaldehyde (25.30 g),  
15 potassium carbonate (15.20 g), benzyl bromide (21.7 ml) and N,N-dimethylformamide (250 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium  
20 chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-benzyloxy-4-hydroxybenzaldehyde (24.62 g, yield 59%) was obtained from a fraction eluted with ethyl acetate-hexane-chloroform (3:10:12, volume ratio). The crystals were  
25 recrystallized from ethanol. melting point: 123-124°C.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 5.21 (2H, s), 5.79 (1H, s), 7.04 (1H, d, J=8.3 Hz), 7.38-7.47 (7H, m), 9.84 (1H, s).

【0134】

#### Reference Example 90

A mixture of 3-benzyloxy-4-hydroxybenzaldehyde (10.60 g),  
30 potassium carbonate (12.84 g), chloromethyl methyl ether (5.2 ml) and N,N-dimethylformamide (150 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with toluene. The  
35 toluene layer was washed with saturated aqueous sodium

chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). To a mixture of the  
5 obtained oily substance, ethyl diethylphosphonoacetate (12.38 g) and N,N-dimethylformamide (90 ml) was added sodium hydride (60%, in oil, 2.43 mg) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl  
10 acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-[3-benzyloxy-4-(methoxymethoxy)phenyl]propenoate (13.48 g, yield 85%) was obtained as a pale-yellow oily substance  
15 from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.33 (3H, t, J=7.1 Hz), 3.53 (3H, s), 4.25 (2H, q, J=7.1 Hz), 5.19 (2H, s), 5.25 (2H, s), 6.30 (1H, d, J=15.9 Hz), 6.90 (1H, d, J=8.5 Hz), 7.10 (1H, dd, J=8.3, 2.2  
20 Hz), 7.29-7.44 (5H, m), 7.59 (1H, d, J=15.9 Hz), 9.84 (1H, s).

#### Reference Example 91

A mixture of ethyl (E)-3-[3-benzyloxy-4-(methoxymethoxy)phenyl]propenoate (13.48 g), 5% palladium-carbon (1.35 g) and ethanol (60 ml) was stirred overnight at  
25 room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated to give a residue. A mixture of the obtained residue, potassium carbonate (10.88 g), benzyl bromide (5.1 ml) and N,N-dimethylformamide (50 ml) was stirred overnight at room  
30 temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[3-benzyloxy-4-  
35 (methoxymethoxy)phenyl]propionate (9.46 g, yield 70%) was

obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.23 (3H, t, J=7.2 Hz), 2.58 (2H, d, J=7.8 Hz), 2.87 (2H, t, J=7.8 Hz), 3.52 (3H, s), 4.12 (2H, q, J=7.1 Hz), 5.12 (2H, s), 5.21 (2H, s), 6.76 (1H, dd, J=8.3, 2.0 Hz), 6.83 (1H, d, J=8.1 Hz), 6.99 (1H, d, J=2.2 Hz), 7.27-7.44 (5H, m).

#### Reference Example 92

To a mixture of ethyl 3-[3-benzyloxy-4-(methoxymethoxy)phenyl]propionate (9.46 g) and ethanol (100 ml) was added hydrochloric acid (3 drops) with a pipette, and the mixture was stirred at 80°C for 1 hour. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(3-benzyloxy-4-hydroxyphenyl)propionate (8.13 g, yield 99%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). melting point: 60-61°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.24 (3H, t, J=7.1 Hz), 2.57 (2H, d, J=7.9 Hz), 2.86 (2H, t, J=7.8 Hz), 4.12 (2H, q, J=7.2 Hz), 5.08 (2H, s), 5.62 (1H, s), 6.66 (1H, dd, J=8.1, 2.2 Hz), 6.80 (1H, d, J=2.2 Hz), 6.83 (1H, d, J=8.1 Hz), 7.33-7.43 (5H, m).

[0135]

#### Reference Example 93

A mixture of ethyl (E)-3-(2-benzyloxy-3-methoxyphenyl)propenoate (6.65 g), 5% palladium-carbon (2.46 g) and tetrahydrofuran (100 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(2-hydroxy-3-methoxyphenyl)propionate (5.86 g, yield 88%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.23 (3H, t, J=7.0 Hz), 2.58-2.69 (2H, m), 2.90-3.01 (2H, m), 3.88 (3H, s), 4.13 (2H, q, J=7.0 Hz), 5.84 (1H, s), 6.72-6.78 (3H, m).

#### Reference Example 94

A mixture of 2-hydroxy-5-methoxybenzaldehyde (10.25 g), benzyl bromide (8.1 ml), potassium carbonate (13.93 g) and N,N-dimethylformamide (100 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). To a mixture of the colorless oil, ethyl diethylphosphonoacetate (15.66 g) and N,N-dimethylformamide (100 ml) was added sodium hydride (60%, in oil, 2.73 g) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(2-benzyloxy-5-methoxyphenyl)propenoate (16.58 g, yield 79%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.33 (3H, t, J=7.0 Hz), 3.78 (3H, s), 4.26 (2H, q, J=7.0 Hz), 5.11 (2H, s), 6.49 (1H, d, J=16.0 Hz), 6.80-6.94 (2H, m), 7.04-7.11 (1H, m), 7.26-7.48 (5H, m), 8.06 (1H, d, J=16.0 Hz).

#### Reference Example 95

A mixture of ethyl (E)-3-(2-benzyloxy-5-methoxyphenyl)propenoate (6.83 g), 5% palladium-carbon (1.11 g) and tetrahydrofuran (100 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(2-hydroxy-5-methoxyphenyl)propionate (4.54 g, yield

92%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.23 (3H, t,  $J=7.2$  Hz), 2.68-2.74 (2H, m), 2.83-2.89 (2H, m), 3.74 (3H, s), 4.13 (2H, q,  $J=7.2$  Hz), 6.62-  
5 6.70 (2H, m), 6.83 (1H, d,  $J=8.4$  Hz), 6.95-6.98 (1H, br s).

【0136】

#### Reference Example 96

A mixture of 2-hydroxy-4-methoxybenzaldehyde (25.16 g), benzyl bromide (20 ml), potassium carbonate (25.03 g) and N,N-  
10 dimethylformamide (300 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue  
15 was subjected to silica gel column chromatography, and 2-benzyloxy-4-methoxybenzaldehyde (37.18 g, yield 93%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.86 (3H, s), 5.17 (2H, s), 6.50-6.62 (2H, m),  
20 7.24-7.50 (5H, m), 7.85 (1H, d,  $J=8.4$  Hz), 10.39 (1H, s).

#### Reference Example 97

To a mixture of 2-benzyloxy-4-methoxybenzaldehyde (5.00 g), ethyl diethylphosphonoacetate (4.75 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in  
25 oil, 0.84 g) at  $0^\circ\text{C}$ , and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and  
30 concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(2-benzyloxy-4-methoxyphenyl)propenoate (5.48 g, yield 85%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

35  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.32 (3H, t,  $J=6.8$  Hz), 3.80 (3H, s), 4.23

(2H, q, J=6.8 Hz), 5.15 (2H, s), 6.37-6.56 (3H, m), 7.24-7.53 (6H, m), 8.00 (1H, d, J=16.2 Hz).

#### Reference Example 98

A mixture of ethyl (E)-3-(2-benzyloxy-4-methoxyphenyl)propenoate (5.45 g), 5% palladium-carbon (1.16 g) and tetrahydrofuran (100 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(2-hydroxy-4-methoxyphenyl)propionate (3.80 g, yield 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.24 (3H, t, J=7.0 Hz), 2.57-2.68 (2H, m), 2.77-2.88 (2H, m), 3.76 (3H, s), 4.15 (2H, q, J=7.0 Hz), 6.40-6.52 (2H, m), 6.97 (1H, d, J=8.0 Hz), 7.58 (1H, br s).

【0137】

#### Reference Example 99

To a solution of 2-benzyloxy-4-methoxybenzaldehyde (13.15 g) in tetrahydrofuran (100 ml) was added lithium aluminum hydride (1.50 g) at 0°C, and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added sodium sulfate 10 hydrate (15.09 g), and the mixture was stirred at room temperature for 1 hour. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 2-benzyloxy-4-methoxybenzyl alcohol (12.84 g, yield 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.19 (1H, br t), 3.79 (3H, s), 4.66 (2H, d, J=5.8 Hz), 5.09 (2H, s), 6.44-6.56 (2H m), 7.16-7.46 (6H, m).

#### Reference Example 100

To a mixture of 2-benzyloxy-4-methoxybenzyl alcohol (12.25 g), acetone cyanohydrin (5.70 g), triphenylphosphine (20.03 g) and tetrahydrofuran (200 ml) was dropwise added a 40% toluene solution (32.75 g) of diethyl azodicarboxylate at

room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and (2-benzyloxy-4-methoxyphenyl)acetonitrile (10.34 g, yield 81%) was obtained  
5 as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.65 (2H, s), 3.79 (3H, s), 5.08 (2H, s), 6.43-6.56 (2H, m), 7.22-7.48 (6H, m).

#### Reference Example 101

10 A mixture of (2-benzyloxy-4-methoxyphenyl)acetonitrile (10.34 g), 8 N aqueous sodium hydroxide solution (50 ml) and ethanol (200 ml) was stirred under reflux overnight. After cooling, the reaction mixture was acidified by slowly adding conc. hydrochloric acid (350 ml). After concentration, the  
15 residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. A mixture of the residue, a 10% solution (200 ml) of hydrochloric acid in methanol and methanol (200 ml) was stirred overnight at  
20 room temperature. After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-  
25 benzyloxy-4-methoxyphenyl)acetate (9.35 g, yield 80%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.61 (2H, s), 3.63 (3H, s), 3.78 (3H, s), 5.06 (2H, s), 6.43-6.54 (2H, m), 7.11 (1H, d,  $J=8.0$  Hz), 7.24-7.46  
30 (5H, m).

【0138】

#### Reference Example 102

A mixture of methyl (2-benzyloxy-4-methoxyphenyl)acetate (9.35 g), 5% palladium-carbon (1.44 g) and tetrahydrofuran  
35 (100 ml) was stirred overnight at room temperature under a

hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-hydroxy-4-methoxyphenyl)acetate (6.11 g, yield 95%) was

5 obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.62 (2H, s), 3.75 (3H, s), 3.77 (3H, s), 6.45 (1H, dd,  $J=2.4, 8.4$  Hz), 6.53 (1H, d,  $J=2.4$  Hz), 6.98 (1H, d,  $J=8.4$  Hz), 7.62 (1H, s).

#### 10 **Reference Example 103**

A mixture of 2-hydroxy-3-methoxybenzaldehyde (8.50 g), benzyl bromide (6.7 ml), potassium carbonate (11.66 g) and N,N-dimethylformamide (100 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute  
15 hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and 2-benzyloxy-3-methoxybenzaldehyde (13.08 g, yield 97%) was  
20 obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.95 (3H, s), 5.18 (2H, s), 7.10-7.21 (2H, m), 7.32-7.43 (6H, m), 10.23 (1H, s).

#### **Reference Example 104**

25 To a mixture of 2-benzyloxy-3-methoxybenzaldehyde (5.51 g), ethyl diethylphosphonoacetate (6.12 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 1.03 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water,  
30 and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(2-benzyloxy-3-methoxyphenyl)propenoate (6.68 g, yield 94%) was obtained as a  
35



colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.33 (3H, t,  $J=7.0$  Hz), 3.90 (3H, s), 4.24 (2H, q,  $J=7.0$  Hz), 5.02 (2H, s), 6.38 (1H, d,  $J=16.4$  Hz),  
5 6.92-7.18 (3H, m), 7.28-7.52 (5H, m), 7.98 (1H, d,  $J=16.4$  Hz).

【0139】

#### Reference Example 105

A mixture of [3-(benzyloxy)-1-methyl-1H-pyrazol-5-yl]acetonitrile (5.08 g), 6N aqueous sodium hydroxide solution  
10 (30 ml), tetrahydrofuran (30 ml) and methanol (30 ml) was stirred at 80°C for 2.5 days. The reaction mixture was neutralized with 1N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and  
15 concentrated to give a brown oily substance. To a mixture of the obtained oily substance, potassium carbonate (6.12 g) and N,N-dimethylformamide (230 ml) was added methyl iodide (2.76 ml) at room temperature, and the mixture was stirred overnight. The reaction mixture was poured into saturated  
20 aqueous ammonium chloride solution, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and methyl [3-(benzyloxy)-1-methyl-1H-pyrazol-  
25 5-yl]acetate (1.60 g, yield 28%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.60 (2H, s), 3.68 (3H, s), 3.72 (3H, s), 5.15 (2H, s), 5.62 (1H, s), 7.26 - 7.46 (5H, m).

#### 30 Reference Example 106

A mixture of methyl [3-(benzyloxy)-1-methyl-1H-pyrazol-5-yl]acetate (1.60 g), 5% palladium-carbon (320 mg) and ethanol (100 ml) was stirred at room temperature for 2.5 hours under a hydrogen atmosphere. Palladium-carbon was removed by  
35 filtration and the filtrate was concentrated to give methyl

(3-hydroxy-1-methyl-1H-pyrazol-5-yl)acetate (1.02 g, yield 97%) as a yellow solid. The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 147-148°C.

**5 Reference Example 107**

To a mixture of 3-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)-1-propanol (6.75 g), ethyl 2-(3-hydroxyphenoxy)-2-methylpropanoate (6.39 g), tributylphosphine (12.9 ml) and tetrahydrofuran (1.00L) was added 1,1'-  
10 azodicarbonyldipiperidine (13.1 g) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 2-{3-[3-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy}-2-methylpropanoate (9.47 g,  
15 yield 78%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.24 (3H, t, J = 7.2 Hz), 1.35 (3H, t, J = 6.9 Hz), 1.59 (6H, s), 1.92 - 2.03 (2H, m), 2.45 - 2.55 (2H, m), 3.86 - 3.94 (2H, m), 4.18 - 4.28 (4H, m), 5.07 (2H, s), 6.35 -  
20 6.44 (2H, m), 6.49 - 6.54 (1H, m), 6.96 (1H, s), 7.06 - 7.12 (1H, m), 7.14 - 7.18 (2H, m), 7.26 - 7.36 (3H, m).

**[0140]**

**Reference Example 108**

A mixture of 1-benzyl-4-[3-(1,3-dioxolan-2-yl)propyl]-1H-  
25 pyrazol-3-ol (21.8 g), diethylsulfuric acid (17.3 ml), potassium carbonate (16.7 g) and N,N-dimethylformamide (150 ml) was stirred overnight at room temperature. The reaction mixture was poured into saturated aqueous ammonium hydrochloride solution, and extracted with ethyl acetate. The  
30 ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 1-benzyl-4-[3-(1,3-dioxolan-2-yl)propyl]-3-ethoxy-1H-pyrazole (19.5 g, 82%) was obtained as a yellow oily substance from a  
35 fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.36 (3H, t, J = 6.9 Hz), 1.57 - 1.74 (4H, m), 2.32 - 2.39 (2H, m), 3.80 - 3.98 (4H, m), 4.22 (2H, q, J = 6.9 Hz), 4.82 - 4.87 (1H, m), 5.07 (2H, s), 6.93 (1H, s), 7.13 - 7.17 (2H, m), 7.23 - 7.35 (3H, m).

5 **Reference Example 109**

To a mixture of ethyl 4-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)-1-butanol (1.50 g), ethyl 2-(3-hydroxyphenoxy)-2-methylpropanoate (1.35 g), tributylphosphine (2.73 ml) and tetrahydrofuran (110 ml) was added 1,1'-  
10 azodicarbonyldipiperidine (2.76 g) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 2-{3-[4-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)butoxy]phenoxy}-2-methylpropanoate (1.33 g, yield  
15 52%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.24 (3H, t, J = 7.0Hz), 1.37 (3H, t, J = 7.0 Hz), 1.48 - 1.87 (4H, m), 1.59 (6H, s), 2.33 - 2.43 (2H, m), 3.86 - 3.95 (2H, m), 4.16 - 4.29 (4H, m), 5.09 (2H, s), 6.34 -  
20 6.44 (2H, m), 6.48 - 6.56 (1H, m), 6.95 (1H, s), 7.04 - 7.20 (3H, m), 7.24 - 7.39 (3H, m).

**Reference Example 110**

To a solution of potassium tert-butoxide (3.79 g) in 1,2-dimethoxyethane (17 ml) was dropwise added a solution of  
25 toluenesulfonylmethyl isocyanide (3.29 g) in 1,2-dimethoxyethane (17 ml) at -78°C. Then a solution of 5-(benzyloxy)-2-methoxybenzaldehyde (3.90 g) in 1,2-dimethoxyethane (50 ml) was dropwise added at the same temperature, and the reaction mixture was warmed to room  
30 temperature. The mixture was stirred at room temperature for 1 hour and methanol (85 ml) was added. The reaction mixture was heated until reflux and the mixture was stirred at said temperature for 2 hours. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and extracted with  
35 ethyl acetate. The ethyl acetate layer was washed with

saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and [5-(benzyloxy)-2-methoxyphenyl]acetonitrile (3.63 g, yield 89%) was obtained as  
5 a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.66 (2H, s), 3.81 (3H, s), 5.02 (2H, s), 6.79 (1H, d, J = 9.0 Hz), 6.88 (1H, dd, J = 2.7, 9.0 Hz), 7.03 (1H, d, J = 2.7 Hz), 7.28 - 7.44 (m, 5H).

10     **[0141]**

#### **Reference Example 111**

A mixture of [5-(benzyloxy)-2-methoxyphenyl]acetonitrile (3.63 g), 6N aqueous sodium hydroxide solution (40 ml), tetrahydrofuran (40 ml) and methanol (40 ml) was stirred at  
15 80°C for 3 days. The reaction mixture was neutralized with 1N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated to give a pale-yellow solid. To a mixture of the obtained solid,  
20 potassium carbonate (3.95 g) and N,N-dimethylformamide (478 ml) was added methyl iodide (1.78 ml) at room temperature, and the mixture was stirred overnight. Dilute hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
25 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl [5-(benzyloxy)-2-methoxyphenyl]acetate (3.76 g, yield 92%) was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio)  
30 as a brown solid. The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 74-75°C.

#### **Reference Example 112**

A mixture of methyl [5-(benzyloxy)-2-methoxyphenyl]acetate (3.61 g), 5% palladium-carbon (800 mg)

and ethanol (150 ml) was stirred at room temperature for 4.5 hours under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and  
5 methyl (5-hydroxy-2-methoxyphenyl)acetate (2.40 g, yield 97%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.58 (2H, s), 3.70 (3H, s), 3.75 (3H, s), 5.21 (1H, s), 6.66 - 6.76 (3H, m).

10 **Reference Example 113**

To a mixture of ethyl 2-{3-[3-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy}-2-methylpropanoate (9.47 g), 5% palladium-carbon (10.0 g) and ethanol (200 ml) was added formic acid (65 ml) and the mixture was stirred overnight  
15 while heating under reflux. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 2-{3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy}-2-methylpropanoate (5.10 g, yield 69%) was obtained as a yellow  
20 oily substance from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.25 (3H, t, J = 7.0 Hz), 1.37 (3H, t, J = 6.8 Hz), 1.60 (6H, s), 1.91 - 2.09 (2H, m), 2.48 - 2.60 (2H, m), 3.85 - 3.96 (2H, m), 4.16 - 4.30 (4H, m), 6.34 - 6.45 (2H, m),  
25 6.50 - 6.58 (1H, m), 7.04 - 7.17 (2H, m).

**[0142]**

**Reference Example 114**

A mixture of ethyl 3-(3-ethoxy-1H-pyrazol-4-yl)propanoate (7.65 g), sodium hydride (60%, in oil, 1.16 g) and N,N-  
30 dimethylformamide (120 ml) was stirred at room temperature for 30 minutes, and 2-fluoropyridine (2.48 ml) was added. The mixture was stirred at 100°C overnight. To the reaction mixture was added dilute hydrochloric acid, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
35 washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propanoate (1.52 g, yield 22%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.26 (3H, t, J = 7.2 Hz), 1.43 (3H, t, J = 7.2 Hz), 2.57 - 2.65 (2H, m), 2.70 - 2.78 (2H, m), 4.14 (2H, q, J = 7.2 Hz), 4.34 (2H, q, J = 7.2 Hz), 6.98 - 7.06 (1H, m), 7.66 - 7.74 (2H, m), 8.16 (1H, s), 8.27 - 8.31 (1H, m).

#### 10 **Reference Example 115**

To a solution of ethyl 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propanoate (2.90 g) in tetrahydrofuran (100 ml) was dropwise added a 0.93 M solution (22.0 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was cooled to 0°C and a 0.93 M solution (11.0 ml) of diisobutylaluminum hydride in hexane was added dropwise. The reaction mixture was warmed to room temperature and the mixture was stirred for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (2.41 g, yield 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.44 (3H, t, J = 7.2 Hz), 1.73 - 1.90 (3H, m), 2.49 - 2.56 (2H, m), 3.64 - 3.71 (2H, m), 4.37 (2H, q, J = 7.2 Hz), 6.98 - 7.08 (1H, m), 7.67 - 7.75 (2H, m), 8.16 (1H, s), 8.28 - 8.32 (1H, m).

#### **Reference Example 116**

To a mixture of 2-(1,3-dioxolan-2-yl)ethyltetraphenylphosphonium bromide (53.2 g) and N,N-dimethylformamide (500 ml) was added sodium hydride (60%, in

oil, 4.80 g) at 0°C. The reaction mixture was stirred at room temperature for 30 minutes and a solution of 1-benzyl-3-(benzyloxy)-1H-pyrazole-4-carbaldehyde (28.9 g) in N,N-dimethylformamide (100 ml) was added. The mixture was stirred  
5 at room temperature overnight, and at 70°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica  
10 gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 5% palladium-carbon (3.80 g) and ethanol (500 ml) was stirred overnight at room temperature under a hydrogen atmosphere.  
15 Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 1-benzyl-4-[3-(1,3-dioxolan-2-yl)propyl]-1H-pyrazol-3-ol (21.8 g, yield 76%) was obtained as a white solid from a fraction eluted with ethyl acetate-hexane  
20 (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 93-94°C.

**[0143]**

#### **Reference Example 117**

25 A mixture of 1-benzyl-4-[3-(1,3-dioxolan-2-yl)propyl]-3-ethoxy-1H-pyrazole (22.0 g), 1N hydrochloric acid (150 ml), ethanol (150 ml) and tetrahydrofuran (150 ml) was stirred at room temperature for 2.5 hours, and at 50°C for 3 hours. Saturated aqueous ammonium hydrochloride solution was added to  
30 the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 4-(1-benzyl-3-ethoxy-1H-pyrazol-4-  
35 yl)butanal (10.1 g, yield 53%) was obtained as a colorless oil

from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.36 (3H, t, J = 6.9 Hz), 1.79 - 1.91 (2H, m), 2.32 - 2.48 (4H, m), 4.22 (2H, q, J = 6.9 Hz), 5.07 (2H, s),  
5 6.93 (1H, s), 7.13 - 7.18 (2H, m), 7.24 - 7.36 (3H, m), 9.73 (1H, s).

#### Reference Example 118

To a solution of 4-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)butanal (10.1 g) in ethanol (185 ml) was added sodium  
10 borohydride (1.54 g) at room temperature, and the mixture was stirred overnight. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue  
15 was subjected to silica gel column chromatography, and 4-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)-1-butanol (9.44 g, yield 93%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.37 (3H, t, J = 7.0 Hz), 1.52 - 1.69 (4H, m),  
20 2.29 - 2.41 (2H, m), 3.60 - 3.71 (2H, brm), 4.23 (2H, q, J = 7.0 Hz), 5.08 (2H, s), 6.94 (1H, s), 7.13 - 7.21 (2H, m), 7.22 - 7.39 (3H, m).

#### Reference Example 119

To a mixture of ethyl 2-{3-[4-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)butoxy]phenoxy}-2-methylpropanoate (950 mg), 5%  
25 palladium-carbon (950 mg) and ethanol (10 ml) was added formic acid (3.3 ml), and the mixture was stirred while heating under reflux for 3 hours. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected  
30 to silica gel column chromatography, and ethyl 2-{3-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]phenoxy}-2-methylpropanoate (740 mg, yield 93%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.25 (3H, t, J = 7.2 Hz), 1.39 (3, t, J = 7.2  
35 Hz), 1.59 (6H, s), 1.63 - 1.89 (4H, m), 2.38 - 2.46 (2H, m),



3.89 - 3.95 (2H, m), 4.18 - 4.28 (4H, m), 6.35 - 6.43 (2H, m),  
6.49 - 6.55 (1H, m), 7.05 - 7.12 (1H, m), 7.15 (1H, s).

【0144】

#### Reference Example 120

5 To a mixture of 4-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)-1-  
butanol (1.50 g), methyl 3-(4-hydroxy-2-  
ethoxyphenyl)propanoate (1.35 g), tributylphosphine (2.73 ml)  
and tetrahydrofuran (110 ml) was added 1,1'-  
azodicarbonyldipiperidine (2.76 g) at room temperature, and  
10 the mixture was stirred for 2.5 days. The reaction solution  
was concentrated. The residue was subjected to silica gel  
column chromatography, and a yellow oily substance was  
obtained from a fraction eluted with ethyl acetate-hexane  
(1:6, volume ratio). To a mixture of the obtained oily  
15 substance, 5% palladium-carbon (1.80 g) and ethanol (18 ml)  
was added formic acid (6.0 ml) and the mixture was stirred  
while heating under reflux for 7 hours. Palladium-carbon was  
removed by filtration and the filtrate was concentrated. The  
residue was subjected to silica gel column chromatography, and  
20 methyl 3-{2-ethoxy-4-[4-(3-ethoxy-1H-pyrazol-4-  
yl)butoxy]phenyl}propanoate (0.86 g, yield 60%) was obtained  
as a brown oily substance from a fraction eluted with ethyl  
acetate-hexane (1:1, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.35 - 1.45 (6H, m), 1.62 - 1.90 (4H, m), 2.38  
25 - 2.48 (2H, m), 2.53 - 2.64 (2H, m), 2.81 - 2.92 (2H, m), 3.66  
(3H, s), 3.90 - 4.06 (4H, m), 4.21 (2H, q, J = 7.0 Hz), 6.28 -  
6.43 (2H, m), 6.94 - 7.04 (1H, m), 7.17 (1H, s).

#### Reference Example 121

To a mixture of 4-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)-1-  
30 butanol (1.01 g), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-  
yl)propanoate (1.05 g), tributylphosphine (1.83 ml) and  
tetrahydrofuran (75 ml) was added 1,1'-  
azodicarbonyldipiperidine (1.85 g) at room temperature, and  
the mixture was stirred overnight. The reaction solution was  
35 concentrated. The residue was subjected to silica gel column

chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). To a mixture of the obtained oily substance, 5% palladium-carbon (1.73 g) and ethanol (18 ml) was added formic acid (6 ml) and the mixture was stirred overnight while heating under reflux. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]-1-phenyl-1H-pyrazol-5-yl}propanoate (900 mg, yield 57%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.24 (3H, t, J = 7.0 Hz), 1.39 (3H, t, J = 7.0 Hz), 1.64 - 1.87 (4H, m), 2.36 - 2.47 (2H, m), 2.52 - 2.63 (2H, m), 2.88 - 2.99 (2H, m), 4.05 - 4.30 (6H, m), 5.65 (1H, s), 7.15 (1H, s), 7.28 - 7.50 (5H, m).

#### Reference Example 122

A mixture of ethyl 3-(3-ethoxy-1H-pyrazol-4-yl)propanoate (5.00 g), 4-(trifluoromethyl)phenylboric acid (8.95 g), copper(II) acetate (6.42 g), pyridine (3.42 ml) and methylene chloride (120 ml) was stirred overnight at room temperature. The precipitate was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propanoate (2.41 g, yield 29%) was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio) as colorless crystals. The crystals were recrystallized from ethyl acetate-hexane. melting point: 47-48°C.

【0145】

#### Reference Example 123

To a solution of ethyl 3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propanoate (4.31 g) in tetrahydrofuran (120 ml) was dropwise added a 0.93 M solution (39 ml) of diisobutylaluminum hydride in hexane at 0°C and the mixture was stirred at room temperature overnight. The

reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (3.68 g, yield 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.44 (3H, t, J = 7.0 Hz), 1.68 - 1.92 (3H, m), 2.48 - 2.59 (2H, m), 3.62 - 3.75 (2H, brm), 4.37 (2H, q, J = 7.0 Hz), 7.58 - 7.70 (5H, m).

#### Reference Example 124

To a mixture of 4-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)-1-butanol (2.00 g), triethylamine (1.22 ml) and tetrahydrofuran (70 ml) at room temperature was added methanesulfonyl chloride (677 μL), and the mixture was stirred overnight. Triethylamine (2.03 ml) and methanesulfonyl chloride (1.13 ml) were added to the reaction mixture at room temperature and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 4-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)butyl methanesulfonate (2.46 g, yield 96%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.36 (3H, t, J = 6.9 Hz), 1.54 - 1.68 (2H, m), 1.70 - 1.82 (2H, m), 2.32 - 2.40 (2H, m), 2.98 (3H, s), 4.18 - 4.26 (4H, m), 5.07 (2H, s), 6.92 (1H, s), 7.14 - 7.19 (2H, m), 7.24 - 7.36 (3H, m).

#### Reference Example 125

A mixture of ethyl 3-(3-ethoxy-1H-pyrazol-4-yl)propanoate (662 mg), sodium hydride (60%, in oil, 136 mg) and N,N-dimethylformamide (25 ml) was stirred at room temperature for

30 minutes, and a solution of 4-(1-benzyl-3-ethoxy-1H-pyrazol-4-yl)butyl methanesulfonate (1.00 g) in N,N-dimethylformamide (5 ml) was added. The mixture was stirred overnight at room temperature and the reaction mixture was poured into 0.1N  
5 aqueous hydrochloric acid solution. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a  
10 fraction eluted with ethyl acetate-hexane (1:2, volume ratio). To a mixture of the obtained oily substance, 5% palladium-carbon (1.00 g) and ethanol (10 ml) was added formic acid (3 ml) and the mixture was stirred while heating under reflux for 4 hours. Palladium-carbon was removed by filtration and the  
15 filtrate was concentrated. The residue was diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride solution. After drying (MgSO<sub>4</sub>), the mixture was concentrated to give ethyl 3-{3-ethoxy-1-[4-(3-ethoxy-1H-pyrazol-4-yl)butyl]-1H-  
20 pyrazol-4-yl}propanoate (680 mg, yield 63%) as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.23 (3H, t, J = 6.9 Hz), 1.32 - 1.41 (6H, m), 1.44 - 1.56 (2H, m), 1.72 - 1.84 (2H, m), 2.33 - 2.40 (2H, m), 2.48 - 2.56 (2H, m), 2.61 - 2.68 (2H, m), 3.84 - 3.91 (2H, m),  
25 4.10 (2H, q, J = 6.9 Hz), 4.15 - 4.27 (4H, m), 6.96 (1H, s), 7.10 (1H, s).

【0146】

#### Reference Example 126

To a solution of potassium tert-butoxide (5.22 g) in 1,2-  
30 dimethoxyethane (300 ml) was dropwise added a solution of toluenesulfonylmethyl isocyanide (4.54 g) in 1,2-dimethoxyethane (30 ml) at -78°C. After stirring at the same temperature for 10 minutes, a solution of 3-(benzyloxy)-1-methyl-1H-pyrazole-4-carbaldehyde (4.79 g) in 1,2-  
35 dimethoxyethane (60 ml) was added dropwise. The reaction

mixture was warmed to room temperature. Then methanol (120 ml) was added and stirred while heating under reflux for 2.5 hours. The reaction mixture was poured into saturated aqueous ammonium chloride solution, and extracted with ethyl acetate.

5 The ethyl acetate layer was washed with saturated aqueous sodium chloride solution and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure and [3-(benzyloxy)-1-methyl-1H-pyrazol-5-yl]acetonitrile (5.08 g, quantitative) was obtained as a brown oily substance.

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.67 (2H, s), 3.73 (3H, s), 5.16 (2H, s), 5.73 (1H, s), 7.27 - 7.48 (5H, m).

【0147】

#### Reference Example 127

A mixture of 6-methoxysalicylaldehyde (11.20 g), benzyl bromide (8.8 ml), potassium carbonate (15.29 g) and N,N-dimethylformamide (200 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium

15 chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and 2-benzyloxy-6-methoxybenzaldehyde (15.64 g, yield 88%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.91 (3H, s), 5.18 (2H, s), 6.56-6.66 (2H, m), 7.28-7.49 (6H, m), 10.59 (1H, s).

#### Reference Example 128

To a solution of 2-benzyloxy-6-methoxybenzaldehyde (10.44 g) in tetrahydrofuran (100 ml) was added lithium aluminum

30 hydride (1.23 g) at  $0^\circ\text{C}$ , and the mixture was stirred at room temperature for 1 hour. Sodium sulfate 10 hydrate (12.02 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The precipitate was removed by filtration and the filtrate was concentrated. The residue was

35 subjected to silica gel column chromatography, and 2-

benzyloxy-6-methoxybenzyl alcohol (10.21 g, yield 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.50 (1H, t, J=6.6 Hz), 3.86 (3H, s), 4.85  
5 (2H, d, J=6.6 Hz),  
5.11 (2H, s), 6.54-6.66 (2H, m), 7.14-7.48 (6H, m).

#### Reference Example 129

To a mixture of 2-benzyloxy-6-methoxybenzyl alcohol (12.53 g), acetone cyanohydrin (7.27 g), triphenylphosphine  
10 (27.32 g) and tetrahydrofuran (250 ml) was dropwise added a 40% toluene solution (44.65 g) of diethyl azodicarboxylate at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and (2-benzyloxy-6-  
15 methoxyphenyl)acetonitrile (11.46 g, yield 88%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.73 (2H, s), 3.88 (3H, s), 5.13 (2H, s),  
6.52-6.66 (2H, m), 7.17-7.50 (6H, m).

20 [0148]

#### Reference Example 130

A mixture of (2-benzyloxy-6-methoxyphenyl)acetonitrile (11.46 g), 8N aqueous sodium hydroxide solution (40 ml) and ethanol (200 ml) was stirred under reflux overnight. After  
25 cooling, the reaction mixture was acidified by slowly adding conc. hydrochloric acid (30 ml). After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture  
30 of the residue, a 10% solution (200 ml) of hydrochloric acid in methanol and methanol (200 ml) was stirred overnight at room temperature. After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride  
35 solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was

subjected to silica gel column chromatography, and methyl (2-benzyloxy-6-methoxyphenyl)acetate (6.43 g, yield 50%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.63 (3H, s), 3.76 (2H, s), 3.82 (3H, s), 5.08 (2H, s), 6.52-6.64 (2H, m), 7.12-7.40 (6H, m).

#### Reference Example 131

A mixture of methyl (2-benzyloxy-6-methoxyphenyl)acetate (6.43 g), 5% palladium-carbon (1.59 g) and tetrahydrofuran  
10 (100 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (6-hydroxy-2-methoxyphenyl)acetate (4.20 g, yield 95%) was  
15 obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.73 (3H, s), 3.77 (2H, s), 3.81 (3H, s), 6.40-6.62 (2H, m), 6.94 (1H, s), 7.06-7.18 (1H, m).

#### Reference Example 132

20 To a mixture of 2-benzyloxy-6-methoxybenzaldehyde (3.30 g), ethyl diethylphosphonoacetate (3.60 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 0.61 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water,  
25 and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography to give ethyl (E)-3-(2-benzyloxy-6-methoxyphenyl)propenoate (3.86 g, yield 91%) as a colorless  
30 oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.32 (3H, t,  $J=7.0$  Hz), 3.89 (3H, s), 4.24 (2H, q,  $J=7.0$  Hz), 5.18 (2H, s), 6.53-6.62 (2H, m), 6.91 (1H, d,  $J=16.2$  Hz), 7.16-7.47 (6H, m), 8.20 (1H, d,  $J=16.2$  Hz).  
35

【0149】

**Reference Example 133**

A mixture of ethyl (E)-3-(2-benzyloxy-6-methoxyphenyl)propenoate (3.86 g), 5% palladium-carbon (1.00 g) and tetrahydrofuran (50 ml), and the reaction mixture was poured into saturated aqueous ammonium chloride solution. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(6-hydroxy-2-methoxyphenyl)propionate (2.52 g, yield 90%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.22 (3H, t, J=7.0 Hz), 2.65-2.75 (2H, m), 2.83-2.93 (2H, m), 3.80 (3H, s), 4.13 (2H, q, J=7.0 Hz), 6.45 (1H, d, J=8.0 Hz), 6.60 (1H, d, J=8.0 Hz), 7.02-7.14 (1H, m), 7.86 (1H, s).

**Reference Example 134**

To a solution of ethyl 3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propionate (3.92 g) in tetrahydrofuran (25 ml) was dropwise added a 1.0 M solution (25 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (3.15 g, yield 91%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 62-63°C.

**Reference Example 135**

To a solution of 3-benzyloxy-4-ethoxybenzaldehyde (5.34 g) in tetrahydrofuran (50 ml) was added lithium aluminum



hydride (0.40 g) at 0°C, and the mixture was stirred at room temperature for 1 hour. Sodium sulfate 10 hydrate (4.02 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The precipitate was removed by  
5 filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-benzyloxy-4-ethoxybenzyl alcohol (4.88 g, yield 91%) was obtained as a colorless oil from a fraction eluted with ethyl acetate.

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.47 (3H, t, J=7.0 Hz), 4.13 (2H, q, J=7.0 Hz), 4.60 (2H, d, J=5.8 Hz), 5.14 (2H, s), 6.78-6.99 (3H, m), 7.26-7.50 (5H, m).

【0150】

#### Reference Example 136

15 A mixture of ethyl 3-oxoheptanate (10.16 g) and N,N-dimethylformamide dimethyl acetal (9.53 g) were refluxed for 1 hour, and concentrated under reduced pressure. The residue was dissolved in ethanol (250 ml) and a solution of hydrazine hydrate (3.06 g) in ethanol (50 ml) was slowly added at room  
20 temperature, which was followed by stirring overnight. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture  
25 of the residue, 2-chloro-5-(trifluoromethyl)pyridine (11.35 g), potassium carbonate (13.00 g) and N,N-dimethylformamide (200 ml) was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with  
30 saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (17.25 g, yield 86%) was obtained as colorless crystals from a fraction eluted with  
35 ethyl acetate-hexane (1:4, volume ratio). The crystals were

recrystallized from ethyl acetate-hexane. melting point: 58-59°C.

#### Reference Example 137

To a solution of ethyl 3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (16.50 g) in tetrahydrofuran (100 ml) was dropwise added a 1.0 M solution (100 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and {3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (13.59 g, yield 94%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 110-111°C.

#### Reference Example 138

A mixture of {3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (6.00 g), activated manganese dioxide (18.19 g) and tetrahydrofuran (100 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (5.16 g, yield 87%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.97 (3H, t, J=7.4 Hz), 1.34-1.82 (4H m), 2.90-3.04 (2H, m), 8.03-8.17 (2H, m), 8.68-8.73 (1H, m), 9.03 (1H, s), 10.05 (1H, s).

【0151】

#### Reference Example 139

To a mixture of 3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (4.33 g), ethyl

diethylphosphonoacetate (3.95 g) and N,N-dimethylformamide (50 ml) was added, sodium hydride (60%, in oil, 0.64 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (4.81 g, yield 90%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 84-85°C.

#### Reference Example 140

A mixture of ethyl (E)-3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (3.50 g), 5% palladium-carbon (0.73 g) and tetrahydrofuran (50 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (3.31 g, 94%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 63-64°C.

#### Reference Example 141

To a solution of ethyl 3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (3.00 g) in tetrahydrofuran (50 ml) was dropwise added a 1.0 M solution (20 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (2.43 g, yield 91%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 93-94°C.

【0152】

#### Reference Example 142

To a solution of ethyl 3-[3-(1-ethylpropyl)-1H-pyrazol-4-yl]propionate (3.30 g) in N,N-dimethylformamide (40 ml) was added sodium hydride (60%, in oil, 0.57 g) at 0°C and the mixture was stirred at room temperature for 15 minutes. 2,5-Dichloropyridine (2.10 g) was added at room temperature, and stirred overnight at 100°C. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propionate (3.92 g, yield 81%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.86 (6H, t, J=7.2 Hz), 1.26 (3H, t, J=7.2 Hz), 1.60-1.86 (4H, m), 2.48-2.88 (5H, m), 4.16 (2H, q, J=7.2 Hz), 7.69 (1H, d, J=2.6, 8.8 Hz), 7.84-7.92 (1H, m), 8.20 (1H, s), 8.26-8.39 (1H, m).

#### Reference Example 143

A mixture of ethyl 3-(3-propyl-1H-pyrazol-4-yl)propanoate (1.30 g), 4-(trifluoromethyl)phenylboric acid (2.37 g), copper(II) acetate (1.69 g), pyridine (0.9 ml) and N,N-dimethylformamide (50 ml) was stirred overnight at room temperature. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained

from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). To a solution of the obtained colorless oil in tetrahydrofuran (30 ml) was added lithium aluminum hydride (0.23 g) at 0°C, and the mixture was stirred at room  
5 temperature for 1 hour. The sodium sulfate 10 hydrate (2.10 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-  
10 propyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (0.87 g, yield 45%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.02 (3H, t, J=7.0 Hz), 1.36 (1H, br t), 1.64-  
15 1.98 (4H, m), 2.52-2.69 (4H, m), 3.68-3.81 (2H, m), 7.60-7.80 (5H, m).

#### Reference Example 144

A mixture of ethyl 3-isopropyl-1H-pyrazole-4-carboxylate (5.00 g), 4-(trifluoromethyl)phenylboric acid (10.45 g),  
20 copper(II) acetate (7.50 g), pyridine (4.0 ml) and N,N-dimethylformamide (75 ml) was stirred overnight at room temperature. The precipitate was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-isopropyl-1-[4-  
25 (trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylate (6.93 g, yield 77%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane.  
melting point: 74-75°C.

30 [0153]

#### Reference Example 145

To a solution of ethyl 3-isopropyl-1-[4-  
(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylate (6.00 g) in tetrahydrofuran (30 ml) was added lithium aluminum hydride  
35 (0.54 g) at 0°C, and the mixture was stirred at room

temperature for 1 hour. Sodium sulfate 10 hydrate (5.10 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The precipitate was removed by filtration and the filtrate was concentrated. The residue was  
5 subjected to silica gel column chromatography, and {3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methanol (4.86 g, yield 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). The crystals were recrystallized from  
10 ethyl acetate-hexane. melting point: 84-85°C.

#### Reference Example 146

A mixture of {3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methanol (2.35 g), activated manganese dioxide (7.90 g) and tetrahydrofuran (50 ml) was stirred overnight at  
15 room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbaldehyde (2.25 g, yield 96%) was obtained as colorless  
20 crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 81-82°C.

#### Reference Example 147

To a mixture of 3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbaldehyde (2.10 g),  
25 ethyl diethylphosphonoacetate (2.50 g) and N,N-dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 0.36 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was  
30 washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-{3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propenoate (2.47 g,  
35

yield 94%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 118-119°C.

5     **[0154]**

**Reference Example 148**

A mixture of ethyl (E)-3-{3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propenoate (2.30 g), 5% palladium-carbon (0.82 g) and tetrahydrofuran (50 ml) was  
10 stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propionate (2.30  
15 g, 99%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.26 (3H, t, J=7.0 Hz), 1.34 (6H, d, J=6.8 Hz), 2.56-2.67 (2H, m), 2.79-2.90 (2H, m), 2.96-3.13 (1H, m), 4.16 (2H, q, J=7.0 Hz), 7.61-7.80 (5H, m).

20     **Reference Example 149**

To a solution of ethyl 3-{3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propionate (2.30 g) in tetrahydrofuran (20 ml) was added lithium aluminum hydride (0.25 g) at 0°C, and the mixture was stirred at room  
25 temperature for 1 hour. Sodium sulfate 10 hydrate (2.30 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (1.89 g, yield 93%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.34 (6H, d, J=6.8 Hz), 1.80-1.98 (2H, m),  
35 2.53-2.67 (2H, m), 2.94-3.13 (1H, m), 3.68-3.82 (2H, m), 7.61-

7.80 (5H, m).

#### Reference Example 150

A mixture of ethyl 3-cyclohexyl-3-oxopropionate (12.60 g) and N,N-dimethylformamide dimethyl acetal (11.33 g) was  
5 refluxed for 1 hour, and concentrated under reduced pressure. The residue was dissolved in ethanol (150 ml) and a solution of hydrazine hydrate (3.20 g) in ethanol (150 ml) was slowly added at room temperature. The mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure  
10 and the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the residue, 2-chloro-5-(trifluoromethyl)pyridine (12.06 g), potassium carbonate (15.94 g) and N,N-  
15 dimethylformamide (200 ml) was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica  
20 gel column chromatography, and ethyl 3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (20.15 g, yield 86%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane.  
25 melting point: 99-100°C.

【0155】

#### Reference Example 151

To a solution of ethyl 3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (20.00  
30 g) in tetrahydrofuran (150 ml) was dropwise added a 1.0 M solution (120 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate  
35 layer was washed with saturated aqueous sodium chloride



solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (16.39 g, yield 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 138-139°C.

#### Reference Example 152

A mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (7.10 g), activated manganese dioxide (22.90 g) and tetrahydrofuran (100 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (6.69 g, yield 95%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 103-104°C.

#### Reference Example 153

To a mixture of 3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (6.40 g), ethyl diethylphosphonoacetate (5.33 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 0.93 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (7.53 g, yield 96%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 132-133°C.

【0156】

**Reference Example 154**

A mixture of ethyl (E)-3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (7.40 g), 5% palladium-carbon (1.49 g) and tetrahydrofuran (100 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (7.20 g, 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.32-2.00 (13H, m), 2.58-2.88 (5H, m), 4.16 (2H, q, J=7.0 Hz), 7.89-8.05 (2H, m), 8.27 (1H, s), 8.56-8.64 (1H, m).

**Reference Example 155**

To a solution of ethyl 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (7.20 g) in tetrahydrofuran (60 ml) was dropwise added a 1.0 M solution (40 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (5.83 g, yield 91%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 106-107°C.

**Reference Example 156**

To a mixture of 3-benzyloxy-4-ethoxybenzyl alcohol (4.80 g), acetone cyanohydrin (3.50 g), triphenylphosphine (9.86 g) and tetrahydrofuran (100 ml) was dropwise added a 40% toluene

solution (16.16 g) of diethyl azodicarboxylate at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-4-ethoxyphenyl)acetonitrile (3.68 g, yield 74%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.47 (3H, t, J=6.8 Hz), 3.67 (2H, s), 4.12 (2H, q, J=6.8 Hz), 5.15 (2H, s), 6.74-6.96 (3H, m), 7.28-7.47 (5H, m).

【0157】

#### Reference Example 157

A mixture of (3-benzyloxy-4-ethoxyphenyl)acetonitrile (3.68 g), 4N aqueous sodium hydroxide solution (10 ml) and ethanol (50 ml) was stirred under reflux overnight. After cooling, the reaction mixture was acidified by slowly adding conc. hydrochloric acid (5 ml). After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the residue, a 10% solution (20 ml) of hydrochloric acid in methanol and methanol (50 ml) was stirred overnight at room temperature. After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-benzyloxy-4-ethoxyphenyl)acetate (2.99 g, yield 72%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.45 (3H, t, J=7.0 Hz), 3.54 (2H, s), 3.69 (3H, s), 4.11 (2H, q, J=7.0 Hz), 5.13 (2H, s), 6.70-6.88 (3H, m), 7.27-7.48 (5H, m).

#### Reference Example 158

A mixture of methyl (3-benzyloxy-4-ethoxyphenyl)acetate

(2.99 g), 5% palladium-carbon (0.61 g) and tetrahydrofuran (50 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica  
5 gel column chromatography, and methyl (4-ethoxy-3-hydroxyphenyl)acetate (1.89 g, yield 90%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.44 (3H, t,  $J=7.0$  Hz), 3.54 (2H, s), 3.69  
10 (3H, s), 4.11 (2H, q,  $J=7.0$  Hz), 5.61 (1H, s), 6.72-6.89 (3H, m).

#### Reference Example 159

A mixture of 3-fluorosalicylaldehyde (5.20 g), benzyl bromide (4.5 ml), potassium carbonate (5.26 g) and N,N-  
15 dimethylformamide (75 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue  
20 was subjected to silica gel column chromatography, and 2-benzyloxy-3-fluorobenzaldehyde (8.24 g, yield 96%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 5.28 (2H, s), 7.07-7.16 (1H, m), 7.24-7.42  
25 (6H, m), 7.56-7.60 (1H, m), 10.25 (1H, s).

[0158]

#### Reference Example 160

To a solution of 2-benzyloxy-3-fluorobenzaldehyde (8.24 g) in tetrahydrofuran (50 ml) was added lithium aluminum  
30 hydride (0.45 g) at  $0^\circ\text{C}$ , and the mixture was stirred at room temperature for 1 hour. Sodium sulfate 10 hydrate (4.02 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The precipitate was removed by filtration and the filtrate was concentrated. The residue was  
35 subjected to silica gel column chromatography, and 2-

benzyloxy-3-fluorobenzyl alcohol (8.18 g, yield 98%) was obtained as a colorless oil from a fraction eluted with ethyl acetate.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.87 (1H, t, J=6.6 Hz), 4.58 (2H, d, J=6.6 Hz), 5.17 (2H, s), 6.97-7.13 (3H, m), 7.34-7.46 (5H, m).

#### Reference Example 161

To a mixture of 2-benzyloxy-3-fluorobenzyl alcohol (8.10 g), acetone cyanohydrin (4.95 g), triphenylphosphine (18.57 g) and tetrahydrofuran (150 ml) was dropwise added a 40% solution (30.36 g) of diethyl azodicarboxylate in toluene at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and 2-benzyloxy-3-fluorophenylacetonitrile (7.20 g, yield 85%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.56 (2H, s), 5.19 (2H, s), 6.98-7.18 (3H, m), 7.30-7.46 (5H, m).

#### Reference Example 162

A mixture of 2-benzyloxy-3-fluorophenylacetonitrile (7.20 g), 4N aqueous sodium hydroxide solution (10 ml) and ethanol (50 ml) was stirred under reflux overnight. After cooling, the reaction mixture was acidified by slowly adding conc. hydrochloric acid (4 ml). After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the residue, a 10% solution (50 ml) of hydrochloric acid in methanol and methanol (50 ml) was stirred overnight at room temperature. After concentration, the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-benzyloxy-3-fluorophenyl)acetate (6.63 g, yield 81%) was obtained as a

colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 3.62 (5H, s), 5.12 (2H, s), 6.94-7.12 (3H, m), 7.26-7.47 (5H, m).

5     **【0159】**

#### **Reference Example 163**

A mixture of methyl (2-benzyloxy-3-fluorophenyl)acetate (6.63 g), 5% palladium-carbon (1.44 g) and tetrahydrofuran (150 ml) was stirred overnight at room temperature under a  
10 hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-fluoro-2-hydroxyphenyl)acetate (4.53 g, yield 98%) was  
15 acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.58 (1H, br t), 3.71 (2H, s), 3.74 (3H, s), 6.32 (2H, d,  $J=3.4$  Hz), 6.74-7.08 (3H, m).

#### **Reference Example 164**

A mixture of [1-(5-chloro-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]methanol (2.00 g), activated manganese dioxide (6.08 g) and tetrahydrofuran (50 ml) was stirred overnight at room temperature. The insoluble material was removed by  
20 filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 1-(5-chloro-2-pyridyl)-3-isopropyl-1H-pyrazole-4-carbaldehyde (1.84  
25 g, yield 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 69-70°C.

#### **Reference Example 165**

To a mixture of 1-(5-chloro-2-pyridyl)-3-isopropyl-1H-pyrazole-4-carbaldehyde (1.50 g), ethyl  
diethylphosphonoacetate (1.62 g) and N,N-dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 0.27 g) at 0°C and  
35 the mixture was stirred overnight at room temperature. The

reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue  
5 was subjected to silica gel column chromatography, and ethyl (E)-3-[1-(5-chloro-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propenoate (1.83 g, yield 95%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from  
10 ethyl acetate-hexane. melting point: 105-106°C.

【0160】

#### Reference Example 166

A mixture of 2-ethylbutanoic acid (7.03 g), 1,1'-carbonyldiimidazole (10.30 g) and tetrahydrofuran (200 ml) was  
15 refluxed for 1.5 hours. After cooling to room temperature, magnesium chloride (6.66 g) and potassium ethyl malonate (11.90 g) were added and the mixture was refluxed for 1.5 hours. The reaction solution was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl  
20 acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. A mixture of the residue and N,N-dimethylformamide dimethyl acetal (15.00 g) was refluxed for 1 hour, and concentrated under reduced pressure. The residue was dissolved in ethanol (100  
25 ml), and a solution of hydrazine hydrate (3.03 g) in ethanol (30 ml) was slowly added at room temperature. The mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with  
30 saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(1-ethylpropyl)-1H-pyrazole-4-carboxylate (9.83 g, yield 77%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2,  
35 volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.85 (6H, t, J=7.0 Hz), 1.36 (3H, t, J=7.0 Hz), 1.50-1.88 (4H, m), 3.28-3.50 (1H, m), 4.29 (2H, q, J=7.0 Hz), 7.96 (1H, s).

#### Reference Example 167

5 A mixture of ethyl 3-(1-ethylpropyl)-1H-pyrazole-4-carboxylate (5.00 g), 2-chloro-5-(trifluoromethyl)pyridine (4.35 g), potassium carbonate (4.84 g) and N,N-dimethylformamide (75 ml) was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid, and  
10 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (7.45  
15 g, yield 88%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.88 (6H, t, J=7.2 Hz), 1.38 (3H, t, J=7.0 Hz), 1.60-1.95 (4H, m), 3.20-3.40 (1H, m), 4.32 (2H, q, J=7.0 Hz), 7.98-8.17 (2H, m), 8.65-8.70 (1H, m), 8.99 (1H, s).

#### 20 Reference Example 168

To a solution of ethyl 3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (6.58 g) in tetrahydrofuran (50 ml) was dropwise added a 1.0 M solution (40 ml) of diisobutylaluminum hydride in hexane at  
25 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was  
30 subjected to silica gel column chromatography, and {3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (5.16 g, yield 89%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

35 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.88 (6H, t, J=7.4 Hz), 1.42 (1H, t, J=5.2



Hz), 1.66-1.88 (4H, m), 2.60-2.80 (1H, m), 4.64 (2H, d, J=5.2 Hz), 7.93-8.11 (2H, m), 8.50 (1H, s), 8.61-8.65 (1H, m).

**[0161]**

**Reference Example 169**

5 A mixture of {3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (5.00 g), activated manganese dioxide (15.18 g) and tetrahydrofuran (50 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated.  
10 The residue was subjected to silica gel column chromatography, and 3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (4.75 g, yield 95%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.88 (6H, t, J=7.4 Hz), 1.68-1.94 (4H, m), 3.08-3.20 (1H, m), 8.02-8.17 (2H, m), 8.67-8.72 (1H, m), 9.03 (1H, s), 10.03 (1H, s).

**Reference Example 170**

To a mixture of 3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (4.70 g), ethyl  
20 diethylphosphonoacetate (4.06 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 0.66 g) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with  
25 ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl  
30 (E)-3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (5.45 g, yield 95%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.88 (6H, t, J=7.4 Hz), 1.34 (3H, t, J=7.0 Hz), 1.66-1.90 (4H, m), 2.70-2.88 (1H, m), 4.26 (2H, q, J=7.0 Hz), 6.30 (1H, d, J=16.0 Hz), 7.61 (1H, d, J=16.0 Hz), 7.97-  
35

8.14 (2H, m), 8.62-8.69 (1H, m), 8.78 (1H, s).

#### Reference Example 171

A mixture of ethyl (E)-3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (5.45 g), 5% palladium-carbon (1.02 g) and tetrahydrofuran (50 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (5.28 g, 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.87 (6H, t, J=7.2 Hz), 1.27 (3H, t, J=7.0 Hz), 1.64-1.86 (4H, m), 2.51-2.68 (3H, m), 2.76-2.88 (2H, m), 4.16 (2H, q, J=7.0 Hz), 7.90-8.07 (2H, m), 8.29 (1H, s), 8.58-8.62 (1H, m).

[0162]

#### Reference Example 172

To a solution of ethyl 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (5.20 g) in tetrahydrofuran (30 ml) was dropwise added a 1.0 M solution (30 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (4.29 g, yield 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 79-80°C.

#### Reference Example 173

A mixture of 2-methylbutanoic acid (10.27 g), 1,1'-

carbonyldiimidazole (16.48 g) and tetrahydrofuran (200 ml) was refluxed for 1.5 hours. After cooling to room temperature, magnesium chloride (10.58 g) and potassium ethyl malonate (18.92 g) were added and the mixture was refluxed for 1.5  
5 hours. The reaction solution was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. A mixture of the residue and N,N-dimethylformamide dimethyl acetal  
10 (18.05 g) was refluxed for 1 hour, and concentrated under reduced pressure. The residue was dissolved in ethanol (150 ml) and a solution of hydrazine hydrate (5.13 g) in ethanol (50 ml) was slowly added at room temperature. The mixture was stirred overnight. The reaction mixture was concentrated under  
15 reduced pressure and the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(1-methylpropyl)-1H-pyrazole-4-  
20 carboxylate (14.48 g, yield 73%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.91 (3H, t,  $J=7.2$  Hz), 1.31 (3H, d,  $J=7.2$  Hz), 1.36 (3H, t,  $J=7.2$  Hz), 1.50-1.82 (2H, m), 3.44-3.58 (1H, m), 4.29 (2H, q,  $J=7.2$  Hz), 7.94 (1H, s).

#### Reference Example 174

A mixture of ethyl 3-(1-methylpropyl)-1H-pyrazole-4-carboxylate (10.00 g), 2-chloro-5-(trifluoromethyl)pyridine (9.38 g), potassium carbonate (8.66 g) and N,N-  
30 dimethylformamide (100 ml) was stirred overnight at  $100^\circ\text{C}$ . The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica  
35 gel column chromatography, and ethyl 3-(1-methylpropyl)-1-[5-

(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (15.39 g, yield 88%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane.  
5 melting point: 63-64°C.

【0163】

#### Reference Example 175

To a solution of ethyl 3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (13.44 g) in tetrahydrofuran (100 ml) was dropwise added a 1.0 M  
10 solution (90 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate  
15 layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and {3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (10.86 g, yield 92%) was obtained as colorless  
20 crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 76-77°C.

#### Reference Example 176

A mixture of {3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (8.00 g), activated  
25 manganese dioxide (24.16 g) and tetrahydrofuran (100 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography,  
30 and 3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (7.39 g, yield 93%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 82-83°C.

#### 35 Reference Example 177

To a mixture of 3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (6.50 g), ethyl diethylphosphonoacetate (5.06 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 0.88 g) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (7.59 g, yield 95%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 75-76°C.

【0164】

#### Reference Example 178

A mixture of ethyl (E)-3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (7.30 g), 5% palladium-carbon (1.48 g) and tetrahydrofuran (50 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (7.21 g, 98%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.92 (3H, t, J=7.2 Hz), 1.20-1.34 (6H, m), 1.54-1.90 (2H, m), 2.58-2.68 (2H, m), 2.76-2.87 (3H, m), 4.16 (2H, q, J=7.2 Hz), 7.90-8.05 (2H, m), 8.28 (1H, s), 8.57-8.63 (1H, m).

#### Reference Example 179

To a solution of ethyl 3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (7.20

g) in tetrahydrofuran (50 ml) was dropwise added a 1.0 M solution (50 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (6.09 g, yield 95%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 72-73°C.

#### Reference Example 180

A mixture of 2-methylpentanoic acid (11.65 g), 1,1'-carbonyldiimidazole (17.89 g) and tetrahydrofuran (200 ml) was refluxed for 1.5 hours. After cooling to room temperature, magnesium chloride (10.48 g) and potassium ethoxycarbonylacetate (18.75 g) were added and the mixture was refluxed for 1.5 hours. The reaction solution was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the residue and N,N-dimethylformamide dimethylacetal (17.90 g) was refluxed for 1 hour, and concentrated under reduced pressure. The residue was dissolved in ethanol (200 ml), and a solution of hydrazine hydrate (5.10 g) in ethanol (50 ml) was slowly added at room temperature. The mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The obtained ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(1-methylbutyl)-1H-pyrazole-4-carboxylate (16.85 g, yield

80%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.90 (3H, t, J=7.0 Hz), 1.18-1.44 (6H, m), 1.48-1.80 (4H, m), 3.52-3.70 (1H, m), 4.30 (2H, q, J=7.0 Hz),  
5 7.94 (1H, s).

【0165】

#### Reference Example 181

A mixture of ethyl 3-(1-methylbutyl)-1H-pyrazole-4-carboxylate (6.50 g), 2-chloro-5-(trifluoromethyl)pyridine  
10 (5.85 g), potassium carbonate (5.09 g) and N,N-dimethylformamide (100 ml) was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
15 (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (9.71 g, yield 88%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.91 (3H, t, J=7.2 Hz), 1.23-1.92 (10H, m), 3.44-3.59 (1H, m), 4.32 (2H, q, J=7.2 Hz), 8.00-8.15 (2H, m), 8.65-8.69 (1H, m), 8.97 (1H, s).

#### Reference Example 182

To a solution of ethyl 3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carboxylate (9.71  
25 g) in tetrahydrofuran (100 ml) was dropwise added a 1.0 M solution (60 ml) of diisobutyl aluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric  
30 acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and {3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-  
35 yl}methanol (8.21 g, yield 96%) was obtained as a colorless

oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.91 (3H, t, J=6.8 Hz), 1.27-1.90 (8H, m), 2.88-3.10 (1H, m), 4.65 (2H, d, J=6.2 Hz), 7.93-8.10 (2H, m),  
5 8.48 (1H, s), 8.60-8.66 (1H, m).

#### Reference Example 183

A mixture of 3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (8.21 g), activated manganese dioxide (26.48 g) and tetrahydrofuran (100 ml) was  
10 stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (7.56 g, yield 93%) was obtained as  
15 colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 63-64°C.

【0166】

#### Reference Example 184

To a mixture of 3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazole-4-carbaldehyde (7.40 g), ethyl diethylphosphonoacetate (5.50 g) and N,N-dimethylformamide (70 ml) was added sodium hydride (60%, in oil, 0.96 g) at 0°C, and the mixture was stirred overnight at room temperature. The  
25 reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl  
30 (E)-3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (8.15 g, yield 90%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.92 (3H, t, J=7.2 Hz), 1.24-1.45 (8H, m),  
35 1.56-1.88 (2H, m), 2.98-3.14 (1H, m), 4.27 (2H, q, J=7.2 Hz),



6.29 (1H, d, J=16.2 Hz), 7.62 (1H, d, J=16.2 Hz), 7.98-8.13 (2H, m), 8.64-8.70 (1H, m), 8.76 (1H, s).

#### Reference Example 185

A mixture of ethyl (E)-3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propenoate (8.15 g), 5% palladium-carbon (1.33 g) and tetrahydrofuran (75 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (8.10 g, 99%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.91 (3H, t, J=7.4 Hz), 1.22-1.90 (10H, m), 2.58-2.68 (2H, m), 2.76-2.98 (3H, m), 4.16 (2H, q, J=7.0 Hz), 7.90-8.06 (2H, m), 8.28 (1H, s), 8.58-8.63 (1H, m).

#### Reference Example 186

To a solution of ethyl 3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propionate (8.10 g) in tetrahydrofuran (50 ml) was dropwise added a 1.0 M solution (50 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (6.63 g, yield 92%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 72-73°C.

【0167】

#### Reference Example 187

To a solution of 3-isopropyl-4-[3-

(methoxymethoxy)propyl]-1H-pyrazole (0.90 g) in N,N-dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 0.17 g) at 0°C and the mixture was stirred at room temperature for 15 minutes. 2,3-Dichloro-5-(trifluoromethyl)pyridine (0.93 g) was added at room temperature and the mixture was stirred overnight at 50°C. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 1-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (1.59 g, yield 96%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.35 (6H, d, J=7.0 Hz), 1.88-2.00 (2H, m), 2.55-2.66 (2H, m), 2.97-3.15 (1H, m), 3.38 (3H, s), 3.58-3.67 (2H, m), 4.65 (2H, s), 8.01 (1H, s), 8.02-8.09 (1H, m), 8.57-8.61 (1H, m).

#### Reference Example 188

A mixture of 1-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (1.59 g), conc. hydrochloric acid (0.05 ml) and methanol (50 ml) was refluxed for 2 hours. The mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. An ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{1-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl}-1-propanol (1.33 g, yield 94%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 66-67°C.

#### Reference Example 189

To a solution of 3-isopropyl-4-[3-

(methoxymethoxy)propyl]-1H-pyrazole (0.98 g) in N,N-dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 0.19 g) at 0°C and the mixture was stirred at room temperature for 15 minutes. 2,5-Dibromopyridine (1.15 g) was  
5 added at room temperature, and the mixture was stirred overnight at 100°C. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was  
10 subjected to silica gel column chromatography, and 1-(5-bromo-2-pyridyl)-3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (1.63 g, yield 96%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.32 (6H, d, J=7.0 Hz), 1.84-2.02 (2H, m), 2.52-2.64 (2H, m), 2.94-3.10 (1H, m), 3.38 (3H, s), 3.55-3.66 (2H, m), 4.65 (2H, s), 7.81-7.85 (2H, m), 8.19 (1H, s), 8.36-8.39 (1H, m).

【0168】

20 **Reference Example 190**

A mixture of 1-(5-bromo-2-pyridyl)-3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (1.63 g), conc. hydrochloric acid (0.05 ml) and methanol (50 ml) was refluxed for 2 hours. The mixture was concentrated under reduced  
25 pressure and the residue was dissolved in ethyl acetate. An ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and  
30 3-[1-(5-bromo-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (1.32 g, yield 92%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 96-97°C.

**Reference Example 191**

35 A mixture of ethyl 3-(1-ethylpropyl)-1H-pyrazole-4-

carboxylate (41.42 g), benzyl bromide (25 ml), potassium carbonate (30.00 g) and N,N-dimethylformamide (200 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 1-benzyl-3-(1-ethylpropyl)-1H-pyrazole-4-carboxylate (55.62 g, yield 94%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.84 (6H, t, J=7.2 Hz), 1.31 (3H, t, J=7.2 Hz), 1.60-1.88 (4H, m), 3.14-3.32 (1H, m), 4.23 (2H, q, J=7.2 Hz), 5.27 (2H, s), 7.10-7.40 (5H, m), 7.86 (1H, s).

#### Reference Example 192

To a solution of ethyl 1-benzyl-3-(1-ethylpropyl)-1H-pyrazole-4-carboxylate (55.62 g) in tetrahydrofuran (200 ml) was added lithium aluminum hydride (5.38 g) at 0°C, and the mixture was stirred at room temperature for 1 hour. Sodium sulfate 10 hydrate (53.88 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and [1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-4-yl]methanol (47.18 g, yield 99%) was obtained as a colorless oil from a fraction eluted with ethyl acetate.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.84 (6H, t, J=7.4 Hz), 1.22 (1H, br t), 1.60-1.82 (4H, m), 2.48-2.70 (1H, m), 4.52 (2H, d, J=5.0 Hz), 5.26 (2H, s), 7.08-7.42 (6H, m).

【0169】

#### Reference Example 193

A mixture of [1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-4-yl]methanol (47.18 g), activated manganese dioxide (152.00 g) and tetrahydrofuran (300 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration

and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 1-benzyl-3-(1-ethylpropyl)-1H-pyrazole-4-carbaldehyde (42.25 g, yield 90%) was obtained as a colorless oil from a fraction eluted with  
5 ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.85 (6H, t, J=7.4 Hz), 1.67-1.90 (4H, m), 2.88-3.10 (1H, m), 5.29 (2H, s), 7.18-7.41 (5H, m), 7.76 (1H, s), 9.87 (1H, s).

#### Reference Example 194

10 To a mixture of 1-benzyl-3-(1-ethylpropyl)-1H-pyrazole-4-carbaldehyde (42.25 g), ethyl diethylphosphonoacetate (40.70 g) and N,N-dimethylformamide (200 ml) was added sodium hydride (60%, in oil, 6.95 g) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured  
15 into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-[1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propenoate (52.30 g, yield 97%)  
20 was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.83 (6H, t, J=7.2 Hz), 1.30 (3H, t, J=7.2 Hz), 1.60-1.84 (4H, m), 2.64-2.78 (1H, m), 4.21 (2H, q, J=7.2 Hz), 5.27 (2H, s), 6.02 (1H, d, J=15.6 Hz), 7.08-7.42 (5H, m),  
25 7.51 (1H, s), 7.57 (1H, d, J=15.6 Hz).

#### Reference Example 195

A mixture of ethyl (E)-3-[1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propenoate (10.00 g), 5% palladium-carbon (10.26  
30 g), formic acid (50 ml) and ethanol (50 ml) was refluxed for 5 hours. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was dissolved in ethyl acetate, washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was  
35 subjected to silica gel column chromatography, and ethyl 3-[3-

(1-ethylpropyl)-1H-pyrazol-4-yl]propionate (6.60 g, 91%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.82 (6H, t, J=7.4 Hz), 1.25 (3H, t, J=7.4 Hz), 1.50-1.82 (4H, m), 2.48-2.81 (5H, m), 4.14 (2H, q, J=7.4 Hz), 7.36 (1H, s).

**[0170]**

#### **Reference Example 196**

To a solution of 3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (0.90 g) in N,N-dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 0.19 g) at 0°C, and the mixture was stirred at room temperature for 30 minutes. 2,3,5-Trichloropyridine (0.89 g) was added at room temperature, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 1-(3,5-dichloro-2-pyridyl)-3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (1.19 g, yield 78%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.34 (6H, d, J=7 Hz), 1.85-2.00 (2H, m), 2.55-2.65 (2H, m), 2.95-3.15 (1H, m), 3.38 (3H, s), 3.62 (2H, t, J=6 Hz), 4.65 (2H, s), 7.84 (1H, s), 7.86 (1H, d, J=2 Hz), 8.35 (1H, d, J=2 Hz).

#### **Reference Example 197**

A mixture of 1-(3,5-dichloro-2-pyridyl)-3-isopropyl-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (1.18 g), conc. hydrochloric acid (0.1 ml) and methanol (20 ml) was refluxed for 2 hours. The mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. An ethyl acetate solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated to

give 3-[1-(3,5-dichloro-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (1.02 g, yield 99%) as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.34 (6H, d, J=7 Hz), 1.80-2.00 (2H, m), 2.55-2.65 (2H, m), 2.95-3.15 (1H, m), 3.70-3.80 (2H, m), 7.84 (1H, s), 7.86 (1H, d, J=2 Hz), 8.35 (1H, d, J=2 Hz).

#### Reference Example 198

To a mixture of sodium ethoxide (39.58 g) and diisopropyl ether (800 ml) was added a mixture of ethyl valerate (74.21 g) and ethyl formate (50.67 g) at 0°C over 1 hour. The mixture was stirred at room temperature overnight. Acetic acid (66 ml) was added to the reaction mixture over 20 minutes and then hydrazine hydrate (32.0 g) was added over 10 minutes. The mixture was refluxed for 2 hours. Water (150 ml) was added to the reaction mixture and the mixture was stirred at 0°C for 1 hour. The precipitated crystals were collected by filtration, washed with cold water and isopropyl ether, and dried to give gray-white crystals. To a mixture of the obtained crystals, triethylamine (10.1 ml) and tetrahydrofuran (70 ml) was added di-tert-butyl dicarbonate (16.7 ml) and the mixture was stirred overnight at room temperature. The reaction solution was concentrated and water was added to the residue. The resulting crystals were collected by filtration, washed with water and hexane, and dried to give tert-butyl 3-hydroxy-4-propyl-1H-pyrazole-1-carboxylate (10.30 g, yield 66%) as white crystals. melting point: 70-71°C (decomposition).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.95 (3H, t, J=7.3 Hz), 1.55-1.65 (11H, m), 2.35 (2H, t, J=7.4 Hz), 7.62 (1H, br s).

【0171】

#### Reference Example 199

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (660 mg), tert-butyl 3-hydroxy-4-propyl-1H-pyrazole-1-carboxylate (530 mg), tributylphosphine (860 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (1.06 g) at room temperature and the mixture was stirred overnight. The

reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with diethyl ether-hexane (1:4, volume ratio). A mixture of the obtained oily substance and 4N hydrogen chloride ethyl acetate solution (10 ml) was stirred overnight at room temperature. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 4-propyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazole (700 mg, yield 79%). melting point: 127-128°C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.94 (3H, t, J= 7.3Hz), 1.01 (3H, t, J= 7.4Hz), 1.58 (2H, sextet, J= 7.5Hz), 1.73 (2H, sextet, J= 7.5Hz), 2.05-2.14 (2H, m), 2.35 (2H, t, J=7.6 Hz), 2.60-2.67 (4H, m), 7.15 (1H, s), 7.95 (1H, dd, J= 8.7, 2.3Hz), 8.00 (1H, d, J= 8.5Hz), 8.31 (1H, s), 8.59-8.61 (1H. m), 8.89 (1H, br s).

#### Reference Example 200

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (1.00 g), tert-butyl 3-hydroxy-4-propyl-1H-pyrazole-1-carboxylate (790 mg), tributylphosphine (1.31 g) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (1.64 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance and 4N hydrogen chloride ethyl acetate solution (20 ml) was stirred overnight at room temperature. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried



(MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-propyl-1H-pyrazole (1.19 g, yield 89%). melting point: 121-  
5 122°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.94 (3H, t, J= 7.3Hz), 1.42 (3H, t, J= 7.1Hz), 1.57 (2H, sextet, J= 7.4Hz), 2.09 (2H, quintet, J= 7.0Hz), 2.34 (2H, t, J= 7.4Hz), 2.59 (2H, t, J= 7.4Hz), 4.24 (2H, t, J= 6.3Hz), 4.35 (2H, q, J= 7.0Hz), 7.14 (1H, s), 7.80  
10 (1H, d, J= 8.5Hz), 7.90 (1H, dd, J= 8.8, 2.2Hz), 8.20 (1H, s), 8.53-8.55 (1H, m), 8.82 (1H, br s).

#### Reference Example 201

A mixture of cyclohexylhydrazine hydrochloride (20.12 g), dimethyl acetylenedicarboxylate (19.00 g), potassium acetate  
15 (13.11 g), acetic acid (70 ml) and toluene (70 ml) was stirred at 80°C for 3 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. Toluene was added to  
20 the residue, and the resulting solid was removed by filtration. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl 1-cyclohexyl-3-hydroxy-1H-pyrazole-5-carboxylate (11.86 g, yield 40%) was obtained as colorless crystals from a fraction eluted  
25 with ethyl acetate-chloroform (1:6, volume ratio). melting point: 195-196°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.23-1.97 (10H, m), 3.87 (3H, s), 5.00-5.10 (1H, m), 6.14 (1H, s), 10.99 (1H, br s).

【0172】

#### 30 Reference Example 202

A mixture of methyl 1-cyclohexyl-3-hydroxy-1H-pyrazole-5-carboxylate (11.00 g), benzyl bromide (6.10 ml), potassium carbonate (6.80 g) and N,N-dimethylformamide (80 ml) was stirred overnight at room temperature. The reaction mixture  
35 was poured into dilute hydrochloric acid, and extracted with

ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-benzyloxy-1-cyclohexyl-1H-pyrazole-5-carboxylate (15.40 g, quantitative) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.18-1.48 (3H, m), 1.65-1.74 (1H, m), 1.82-1.97 (6H, m), 3.84 (3H, s), 4.94-5.03 (1H, m), 5.17 (2H, s), 6.18 (1H, s), 7.28-7.47 (5H, m).

#### Reference Example 203

To a mixture of lithium aluminum hydride (4.65 g) and tetrahydrofuran (100 ml) was slowly added a solution of methyl 3-benzyloxy-1-cyclohexyl-1H-pyrazole-5-carboxylate (15.40 g) in tetrahydrofuran (10 ml) at  $0^\circ\text{C}$ , and the mixture was stirred at room temperature for 30 minutes. Acetone (20 ml) was slowly added to decompose excess lithium aluminum hydride, and brine (13 ml) was added. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-1-cyclohexyl-1H-pyrazol-5-yl)methanol (13.61 g, yield 97%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). melting point:  $195-196^\circ\text{C}$ .

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20-1.45 (3H, m), 1.55-1.73 (2H, m), 1.84-2.01 (6H, m), 3.97-4.07 (1H, m), 4.57 (2H, d,  $J = 6.1\text{Hz}$ ), 5.15 (2H, s), 5.59 (1H, s), 7.27-7.47 (5H, m).

#### Reference Example 204

A mixture of (3-benzyloxy-1-cyclohexyl-1H-pyrazol-5-yl)methanol (12.50 g), activated manganese dioxide (50.0 g) and tetrahydrofuran (250 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane

(1:3, volume ratio). To a mixture of the obtained oily substance, ethyl diethylphosphonoacetate (6.75 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 1.20 g) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(3-benzyloxy-1-cyclohexyl-1H-pyrazol-5-yl)propenoate (7.72 g, yield 50%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.17-1.49 (6H, m), 1.67-1.76 (1H, m), 1.83-2.02 (6H, m), 4.06-4.15 (1H, m), 4.26 (2H, q, J= 7.1Hz), 5.17 (2H, s), 5.92 (1H, s), 6.27 (1H, d, J= 15.9Hz), 7.28-7.47 (5H, m), 7.55 (1H, d, J= 15.9Hz).

【0173】

#### Reference Example 205

A mixture of ethyl (E)-3-(3-benzyloxy-1-cyclohexyl-1H-pyrazol-5-yl)propenoate (7.70 g), 5% palladium-carbon (1.0 g), tetrahydrofuran (50 ml) and ethanol (50 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated to give ethyl 3-(1-cyclohexyl-3-hydroxy-1H-pyrazol-5-yl)propanoate (5.54 g, yield 96%) as colorless crystals. melting point: 173-174°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.25-1.43 (6H, m), 1.63-1.94 (7H, m), 2.62 (2H, dd, J= 8.7, 6.7Hz), 3.77-3.87 (1H, m), 4.16 (2H, q, J= 7.2Hz), 5.37 (1H, s), 11.93 (1H, br s).

#### Reference Example 206

To a mixture of methyl acetylenedicarboxylate (29.20 g) and methanol (200 ml) was added hydrazine hydrate (10.30 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated to give yellow crystals (28.61 g). To a mixture of the obtained crystals,

triethylamine (29.5 ml) and tetrahydrofuran (200 ml) was added di-tert-butyl dicarbonate (48.6 ml), and the mixture was stirred overnight. The reaction mixture was concentrated. A mixture of the obtained residue, benzyl bromide, potassium carbonate (29.20 g) and N,N-dimethylformamide (200 ml) was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the residue and 4N hydrogen chloride ethyl acetate solution (100 ml) was stirred overnight at room temperature. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-benzyloxy-1H-pyrazole-5-carboxylate (12.10 g, yield 26%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.89 (3H, s), 5.25 (2H, s), 6.26 (1H, s), 7.22-7.47 (5H, m), 10.60 (1H, br s).

#### Reference Example 207

To a mixture of methyl 3-benzyloxy-1H-pyrazole-5-carboxylate (12.10 g) and N,N-dimethylformamide (50 ml) was added sodium hydride (60%, in oil, 1.20 g) at 0°C and the mixture was stirred for 30 minutes. Isopropyl iodide (5.70 ml) was added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-benzyloxy-1-(1-methylethyl)-1H-pyrazole-5-carboxylate (7.34 g, yield 51%) was obtained as a colorless oil from a fraction eluted with ethyl

acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.44 (6H, d, J=6.6 Hz), 3.84 (3H, s), 5.18 (2H, s), 5.41 (1H, septet, J= 6.6Hz), 6.18 (1H, s), 7.27-7.47 (5H, m).

5     **【0174】**

#### **Reference Example 208**

To a mixture of lithium aluminum hydride (1.30 g) and tetrahydrofuran (50 ml) was slowly added a solution of methyl 3-benzyloxy-1-(1-methylethyl)-1H-pyrazole-5-carboxylate (7.34 g) in tetrahydrofuran (5 ml) at 0°C, and the mixture was  
10 stirred at room temperature for 30 minutes. Acetone (20 ml) was slowly added to decompose excess lithium aluminum hydride, and brine (4 ml) was further added. The precipitate was removed by filtration and the filtrate was concentrated. The  
15 residue was subjected to silica gel column chromatography, and [3-benzyloxy-1-(1-methylethyl)-1H-pyrazol-5-yl]methanol (2.63 g, yield 40%) was obtained as a colorless oil from a fraction eluted with acetone-hexane (2:3, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.44 (6H, d, J= 6.6Hz), 1.74 (1H, t, J=6.1 Hz), 4.48 (1H, septet, J=6.6 Hz), 4.57 (2H, d, J= 5.8Hz), 5.15 (2H, s), 7.24-7.50 (5H, m).

#### **Reference Example 209**

A mixture of [3-benzyloxy-1-(1-methylethyl)-1H-pyrazol-5-yl]methanol (2.60 g), activated manganese dioxide (8.0 g) and  
25 tetrahydrofuran (30 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane  
30 (1:3, volume ratio). To a mixture of the obtained oily substance, ethyl diethylphosphonoacetate (1.67 g) and N,N-dimethylformamide (20 ml) was added sodium hydride (60%, in oil, 0.30 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water,  
35 and extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(3-benzyloxy-1-(1-methylethyl)-1H-pyrazol-5-yl)propenoate (1.23 g, yield 37%)  
5 was obtained as a colorless oil from a fraction eluted with diethyl ether-hexane (1:4, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.33 (3H, t, J= 7.1Hz), 1.46 (6H, d, J= 6.6Hz), 4.26 (2H, q, J= 7.2Hz), 4.57 (1H, septet, J= 6.6Hz), 5.17 (2H, s), 5.92 (1H, s), 6.27 (1H, d, J= 15.8Hz), 7.27-7.50  
10 (5H, m), 7.54 (1H, d, J= 15.8Hz).

#### Reference Example 210

A mixture of ethyl (E)-3-(3-benzyloxy-1-(1-methylethyl)-1H-pyrazol-5-yl)propenoate (1.23 g), 5% palladium-carbon (0.2 g) and tetrahydrofuran (10 ml) was stirred overnight at room  
15 temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated to give ethyl 3-(3-hydroxy-1-(1-methylethyl)-1H-pyrazol-5-yl)propanoate (0.88 g, quantitative) as colorless crystals.  
melting point: 123-124°C.

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.27 (3H, t, J= 7.1Hz), 1.42 (6H, d, J= 6.6Hz), 2.57-2.68 (2H, m), 2.80-2.92 (2H, m), 4.16 (2H, q, J= 7.1Hz), 4.32 (1H, septet, J= 6.6Hz), 5.37 (1H, s).

【0175】

#### Reference Example 211

25 A mixture of methyl 4-methyl-3-oxopentanoate (20.00 g) and 1,1-dimethoxytrimethylamine (24.8 g) was refluxed for 2 hours. The reaction mixture was concentrated to give a yellow oily substance. To a mixture of the obtained oily substance and ethanol (200 ml) was added hydrazine hydrate (7.30 g) at  
30 0°C, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated, and the residue was dissolved in ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate and brine in this order, dried (MgSO<sub>4</sub>) and concentrated to give a brown oily substance. A  
35 mixture of the obtained oily substance, benzyl bromide (17.0

ml), potassium carbonate (20.0 g) and N,N-dimethylformamide (200 ml) was stirred at room temperature for 4 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with  
5 saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl 1-benzyl-3-(1-methylethyl)-1H-pyrazole-4-carboxylate (29.93 g, yield 84%) was obtained as a yellow oily substance from a fraction eluted with diethyl  
10 ether-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.31 (6H, d, J= 7.0Hz), 3.30-3.60 (1H, m), 3.76 (3H, s), 5.24 (2H, s), 7.18-7.40 (5H, m), 7.69 (1H, s).

#### Reference Example 212

To a mixture of lithium aluminum hydride (5.50 g) and  
15 tetrahydrofuran (260 ml) was slowly added a solution of methyl 1-benzyl-3-(1-methylethyl)-1H-pyrazole-4-carboxylate (29.93 g) in tetrahydrofuran (40 ml) at 0°C, and the mixture was stirred at room temperature for 30 minutes. Acetone (20 ml) was slowly added to decompose excess lithium aluminum hydride and brine  
20 (15 ml) was added. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and [1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]methanol (25.21 g, yield 94%) was obtained as a colorless oil from a fraction eluted with  
25 acetone-hexane (2:3, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.32 (6H, d, J= 7.0Hz), 1.45 (1H, br s), 3.08 (1H, septet, J= 7.0Hz), 4.54 (2H, br s), 5.22 (2H, s), 7.14-7.40 (6H, m).

#### Reference Example 213

30 A mixture of [1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]methanol (25.00 g), activated manganese dioxide (100.0 g) and tetrahydrofuran (350 ml) was stirred overnight at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected  
35 to silica gel column chromatography, and a colorless oil was

obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). To a mixture of the obtained oily substance, ethyl diethylphosphonoacetate (25.80 g) and N,N-dimethylformamide (180 ml) was added sodium hydride (60%, in oil, 4.60 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl)propenoate (30.25 g, yield 94%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.30 (3H, t, J= 7.3Hz), 1.33 (6H, d, J= 6.8Hz), 3.16 (1H, septet, J= 6.8Hz), 4.21 (2H, q, J= 7.2Hz), 5.25 (2H, s), 6.51 (1H, d, J= 16.0Hz), 7.18-7.40 (5H, m), 7.45 (1H, s), 7.58 (1H, d, J= 16.0Hz).

【0176】

#### Reference Example 214

To a mixture of 2-ethylphenol (12.22 g), tributylamine (7.41 g) and toluene (50 ml) was added tin tetrachloride (2.61 g) and the mixture was stirred at room temperature for 30 minutes. Paraformaldehyde (6.60 g) was added and the mixture was stirred overnight at 100°C. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-ethylsalicylaldehyde (8.20 g, yield 55%) was obtained as a colorless oil from a fraction eluted with hexane.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.23 (3H, t, J=7.6 Hz), 2.70 (2H, q, J=7.6 Hz), 6.96 (1H, t, J=7.6 Hz), 7.93-7.42 (2H, m), 9.89 (1H, s), 11.28 (1H, s).

#### Reference Example 215



To a mixture of lithium aluminum hydride (2.00 g) and tetrahydrofuran (50 ml) was slowly added a solution of ethyl 3-[1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (11.73 g) in tetrahydrofuran (10 ml) at 0°C, and the mixture  
5 was stirred at room temperature for 30 minutes. Acetone (20 ml) was slowly added to decompose excess lithium aluminum hydride, and brine (5.5 ml) was added. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and  
10 3-[1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]-1-propanol (9.95 g, yield 98%) was obtained as a colorless oil from a fraction eluted with acetone-hexane (2:3, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.29 (6H, d, J= 7.0Hz), 1.44 (1H, t, J= 5.3Hz), 1.70-1.85 (2H, m), 2.49 (2H, t, J= 7.7Hz), 2.98 (1H, septet, J= 7.0Hz), 3.67 (2H, q, J= 5.9Hz), 5.22 (2H, s), 7.02 (1H, s), 7.13-7.39 (5H, m).

#### Reference Example 216

To a mixture of 3-[1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]-1-propanol (9.95 g), N-ethyldiisopropylamine (10.0 ml)  
20 and tetrahydrofuran (100 ml) was added chloromethyl methyl ether (5.50 ml) at 0°C and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride  
25 solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 1-benzyl-4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (10.57 g, yield 91%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).  
30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.29 (6H, d, J= 7.0Hz), 1.70-1.88 (2H, m), 2.49 (2H, t, J= 7.7Hz), 2.98 (1H, septet, J= 7.0Hz), 3.34 (3H, s), 3.54 (2H, t, J= 6.4Hz), 4.61 (2H, s), 5.22 (2H, s), 7.01 (1H, s), 7.12-7.38 (5H, m).

【0177】

#### 35 Reference Example 217

A mixture of 1-benzyl-4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (10.57 g), 5% palladium-carbon (2.0 g) and tetrahydrofuran (100 ml) was stirred overnight at 50°C under a hydrogen atmosphere. Palladium-carbon was removed by  
5 filtration and the filtrate was concentrated to give 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (7.44 g, quantitative) as a yellow oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.29 (6H, d, J= 7.0Hz), 1.77-1.94 (2H, m), 2.53 (2H, t, J= 7.7Hz), 3.05 (1H, septet, J= 7.0Hz), 3.38 (3H, s), 3.57 (2H, t, J= 6.4Hz), 4.64 (2H, s), 7.34 (1H, s).  
10

#### Reference Example 218

To a mixture of ethyl 3-[3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (1.00 g), 2-chloro-5-nitropyridine (0.79 g) and N,N-dimethylformamide (10 ml) was added sodium hydride (60%,  
15 in oil, 0.25 g) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was  
20 subjected to silica gel column chromatography, and ethyl 3-[3-(1-methylethyl)-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propanoate (1.26 g, yield 74%) was obtained as yellow crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). melting point: 90-91°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.27 (3H, t, J= 7.2Hz), 1.34 (6H, d, J= 7.0Hz), 2.60-2.72 (2H, m), 2.78-2.90 (2H, m), 3.04 (1H, septet, J= 6.9Hz), 4.17 (2H, q, J= 7.2Hz), 8.05 (1H, d, J= 9.0Hz), 8.30 (1H, s), 8.50 (1H, dd, J= 9.2, 2.6Hz), 9.20 (1H, dd, J= 2.6, 0.6Hz).  
25

#### 30 Reference Example 219

A mixture of ethyl 3-[3-(1-methylethyl)-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propanoate (1.18 g), 5% palladium-carbon (0.15 g), methanol (4 ml) and tetrahydrofuran (4 ml) was stirred overnight at room temperature under a hydrogen  
35 atmosphere. Palladium-carbon was removed by filtration and the

filtrate was concentrated to give ethyl 3-[1-(5-amino-2-pyridyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (0.93 g, yield 94%) as yellow crystals. melting point: 75-76°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.26 (3H, t, J= 7.1Hz), 1.32 (6H, d, J= 6.9Hz), 2.57-2.65 (2H, m), 2.77-2.85 (2H, m), 3.03 (1H, septet, J= 6.9Hz), 3.63 (2H, br s), 4.14 (2H, q, J= 7.2Hz), 7.09 (1H, dd, J= 8.9, 2.9Hz), 7.70 (1H, dd, J= 8.6, 0.8Hz), 7.82 (1H, dd, J= 3.0, 0.6Hz), 8.09 (1H, s).

[0178]

#### 10 Reference Example 220

To a mixture of ethyl 3-[1-(5-amino-2-pyridyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (2.00 g), tetrafluoroboric acid (42%, 4 ml) and 1,4-dioxane (3 ml) was slowly added a solution of sodium nitrite (0.50 g) in water (1 ml) at 0°C and the mixture was stirred for 30 minutes. Cold water (30 ml) was added to the reaction mixture, and the precipitated crystals were collected by filtration, washed with water and air-dried. The obtained crystal was slowly added to toluene (15 ml) heated to 90°C, and the mixture was stirred at 100°C for 30 minutes. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance (1.17 g) was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). To a mixture of the obtained oily substance and tetrahydrofuran (15 ml) was slowly added a 1.5M solution (6.5 ml) of diisobutylaluminum hydride in toluene at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-[1-(5-fluoro-2-pyridyl)-3-(1-

methylethyl)-1H-pyrazol-4-yl]-1-propanol (0.74 g, yield 42%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). melting point: 78-79°C.

5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.32 (6H, d, J= 6.9Hz), 1.83-1.98 (2H, m), 2.58 (2H, t, J= 7.8Hz), 3.02 (1H, septet, J= 6.9Hz), 3.74 (2H, t, J= 5.6Hz), 7.42-7.52 (1H, m), 7.88-7.95 (1H, m), 8.14-8.20 (2H, m).

#### Reference Example 221

10 To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (0.50 g), 6-chloropyridine-3-carbonitrile (0.36 g) and N,N-dimethylformamide (6 ml) was added sodium hydride (60%, in oil, 0.12 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at  
15 80°C for 3 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the obtained residue, conc. hydrochloric acid (2 drops) and methanol (6 ml) was  
20 stirred overnight at 60°C. The reaction mixture was poured into aqueous sodium hydrogen carbonate, and the precipitated crystals were collected by filtration, washed with water and dried to give 6-[4-(3-hydroxypropyl)-3-(1-methylethyl)-1H-pyrazol-1-yl]pyridine-3-carbonitrile (550 mg, 90%) as  
25 colorless crystals. melting point: 105-106°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.32 (6H, d, J= 7.0Hz), 1.47 (1H, br s), 1.82-2.00 (2H, m), 2.53-2.66 (2H, m), 3.03 (1H, septet, J= 6.9Hz), 3.75 (2H, t, J= 6.4Hz), 7.95 (1H, dd, J= 8.6, 2.0Hz), 8.03 (1H, dd, J= 8.6, 1.0Hz), 8.25 (1H, t, J= 0.9Hz), 8.61 (1H, dd,  
30 J= 2.0, 1.0Hz).

#### Reference Example 222

To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.50 g), 2-chloro-5-nitropyridine (1.23 g) and N,N-dimethylformamide (10 ml) was added sodium  
35 hydride (60%, in oil, 0.37 g) at 0°C, and, after termination of

hydrogen generation, the mixture was stirred at 80°C for 3 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
5 (MgSO<sub>4</sub>) and concentrated. A mixture of the obtained residue, conc. hydrochloric acid (2 drops) and methanol (6 ml) was stirred overnight at 60°C. The reaction mixture was poured into aqueous sodium hydrogen carbonate, and the precipitated crystals were collected by filtration, washed with water and  
10 dried to give 3-[3-(1-methylethyl)-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]-1-propanol (1.60 g, 80%) as colorless crystals. melting point: 130-131°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.34 (6H, d, J= 7.0Hz), 1.36 (1H, t, J= 5.0Hz), 1.84-2.00 (2H, m), 2.55-2.67 (2H, m), 3.04 (1H,  
15 septet, J= 6.9Hz), 3.76 (2H, t, J= 6.0Hz), 8.06 (1H, d, J= 9.2Hz), 8.30 (1H, s), 8.51 (1H, dd, J= 9.2, 2.8Hz), 9.20 (1H, dd, J= 2.5, 0.7Hz).

【0179】

#### Reference Example 223

20 To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.52 g), 2-chloro-5-methylpyridine (1.83 g) and N,N-dimethylformamide (15 ml), was added sodium hydride (60%, in oil, 0.43 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at 110°C  
25 overnight. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the obtained residue, conc. hydrochloric acid (2 ml) and methanol (20 ml) was  
30 refluxed of 2 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-[3-(1-  
35 methylethyl)-1-(5-methyl-2-pyridyl)-1H-pyrazol-4-yl]-1-

propanol (0.80 g, 43%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). melting point: 82-83°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.33 (6H, d, J= 7.0Hz), 1.56 (1H, br s), 1.82-  
5 1.97 (2H, m), 2.32 (3H, s), 2.58 (2H, t, J= 7.7Hz), 3.03 (1H, septet, J= 7.0Hz), 3.74 (2H, t, J= 6.4Hz), 7.52-7.60 (1H, m), 7.82 (1H, d, J= 8.4Hz), 8.14-8.16 (1H, m), 8.20 (1H, s).

#### Reference Example 224

To a mixture of 3-[3-(1-methylethyl)-1-(5-nitro-2-  
10 pyridyl)-1H-pyrazol-4-yl]-1-propanol (1.18 g), methyl (3-methoxy-2-hydroxyphenyl)acetate (800 mg), tributylphosphine (1.64 g) and tetrahydrofuran (40 ml) was added 1,1'-azodicarbonyldipiperidine (2.05 g) at room temperature, and the mixture was stirred overnight. The reaction solution was  
15 concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-methoxy-2-{3-[3-(1-methylethyl)-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetate (1.30 g, 50%) was obtained as yellow crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). melting  
20 point: 108-109°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.35 (6H, d, J= 7.0Hz), 2.00-2.17 (2H, m),  
2.71 (2H, t, J= 7.7Hz), 3.07 (1H, septet, J= 6.9Hz), 3.68 (3H, s), 3.85 (2H, s), 4.07 (2H, t, J= 6.2Hz), 6.80-6.90 (2H, m),  
7.02 (1H, dd, J= 8.4, 7.4Hz), 8.06 (1H, d, J= 9.2Hz), 8.35  
25 (1H, s), 8.51 (1H, dd, J= 9.1, 2.5Hz), 9.20 (1H, d, J= 2.2Hz).

#### Reference Example 225

A mixture of methyl (3-methoxy-2-{3-[3-(1-methylethyl)-1-  
(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetate  
(0.88 g), 5% palladium-carbon (0.1 g), methanol (4 ml) and  
30 tetrahydrofuran (4 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-{3-[1-(5-amino-2-pyridyl)-3-(1-methylethyl)-1H-  
35 pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (0.80 g, 95%)

was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.33 (6H, d,  $J = 7.0\text{Hz}$ ), 1.97-2.15 (2H, m), 2.68 (2H, t,  $J = 7.8\text{Hz}$ ), 3.05 (1H, septet,  $J = 6.9\text{Hz}$ ), 3.63 (2H, br s), 3.66 (3H, s), 3.68 (2H, s), 3.83 (3H, s), 4.06 (2H, t,  $J = 6.4\text{Hz}$ ), 6.78-6.88 (2H, m), 6.95-7.27 (2H, m), 7.72 (1H, d,  $J = 8.8\text{Hz}$ ), 7.83 (1H, d,  $J = 2.6\text{Hz}$ ), 8.14 (1H, s).

**[0180]**

#### **Reference Example 226**

10 To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.00 g), 3-chloro-6-(trifluoromethyl)pyridazine (1.03 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.28 g) at  $0^\circ\text{C}$ , and, after termination of hydrogen generation, the mixture was  
15 stirred at room temperature for 3 hours. The reaction mixture was poured into water, and the precipitated crystals were collected by filtration and washed with water. A mixture of the obtained residue, conc. hydrochloric acid (3 drops) and methanol (15 ml) was refluxed for 4 hours. The reaction  
20 mixture was poured into ice water, and the precipitated crystals were collected by filtration, washed with water, dried and subjected to silica gel column chromatography, and 3-{3-(1-methylethyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (1.00 g, 68%) was obtained as  
25 colorless crystals from a fraction eluted with ethyl acetate-chloroform (1:3, volume ratio). melting point:  $113-114^\circ\text{C}$ .  
 $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.33 (6H, d,  $J = 6.6\text{Hz}$ ), 1.42 (1H, t,  $J = 5.1\text{Hz}$ ), 1.84-2.01 (2H, m), 2.63 (2H, t,  $J = 7.9\text{Hz}$ ), 3.05 (1H, septet,  $J = 6.8\text{Hz}$ ), 3.77 (2H, q,  $J = 5.7\text{Hz}$ ), 7.83 (1H, d,  $J = 9.0\text{Hz}$ ), 8.29 (1H, d,  $J = 9.0\text{Hz}$ ), 8.50 (1H, s).

#### **Reference Example 227**

To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.00 g), 3-chloro-6-methoxypyridazine (0.82 g) and N,N-dimethylformamide (15 ml)  
35 was added sodium hydride (60%, in oil, 0.24 g) at  $0^\circ\text{C}$ , and,

after termination of hydrogen generation, the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water, and the precipitated crystals were collected by filtration and washed with water. A mixture of  
5 the obtained wet crystals, conc. hydrochloric acid (3 drops) and methanol (15 ml) was refluxed for 4 hours. The reaction mixture was poured into ice water, and the precipitated crystals were collected by filtration, washed with water, dried and subjected to silica gel column chromatography, and  
10 3-{1-[6-methoxypyridazin-3-yl]-3-(1-methylethyl)-1H-pyrazol-4-yl}-1-propanol (300 mg, 23%) was obtained as a colorless oil from a fraction eluted with acetone-chloroform (1:4, volume ratio). melting point: 122-123°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.32 (6H, d, J= 6.9Hz), 1.39 (1H, t, J= 5.3Hz), 1.84-1.97 (2H, m), 2.60 (2H, t, J= 7.7Hz), 3.03 (1H, septet, J= 7.0Hz), 3.75 (2H, q, J= 5.8Hz), 4.12 (3H, s), 7.06 (1H, d, J= 9.3Hz), 8.11 (1H, d, J= 9.3Hz), 8.32 (1H, s).

#### Reference Example 228

To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.00 g), 6-chloropyridazine-3-carbonitrile (0.72 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.24 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured  
20 into water, and the precipitated crystals were collected by filtration and washed with water. A mixture of the obtained wet crystals, conc. hydrochloric acid (3 drops) and methanol (15 ml) was refluxed for 4 hours. The reaction mixture was poured into ice water, and the precipitated crystals were  
25 collected by filtration, washed with water, dried and subjected to silica gel column chromatography, and 6-[4-(3-hydroxypropyl)-3-(1-methylethyl)-1H-pyrazol-1-yl]pyridazine-3-carbonitrile (950 mg, 74%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-chloroform (1:2,  
30 volume ratio). melting point: 140-141°C.  
35



<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.32 (6H, d, J= 7.0Hz), 1.37 (1H, t, J= 5.1Hz), 1.84-2.01 (2H, m), 2.63 (2H, t, J= 7.9Hz), 3.05 (1H, septet, J= 6.9Hz), 3.77 (2H, q, J= 5.6Hz), 7.82 (1H, d, J= 9.0Hz), 8.25 (1H, d, J= 9.0Hz), 8.48-8.50 (1H, m).

5     **【0181】**

#### **Reference Example 229**

To a mixture of 4-[3-(1-ethylpropyl)-3-(methoxymethoxy)propyl]-1H-pyrazole (2.20 g), 3-chloro-6-(trifluoromethyl)pyridazine (2.17 g) and N,N-dimethylformamide  
10 (30 ml) was added sodium hydride (60%, in oil, 0.48 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium  
15 chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the obtained wet crystals, conc. hydrochloric acid (3 drops) and methanol (50 ml) was refluxed for 4 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with  
20 saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (1.73 g, 55%) was obtained as colorless crystals from a  
25 fraction eluted with ethyl acetate-hexane (1:2, volume ratio). melting point: 86-87°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.87 (6H, d, J= 7.3Hz), 1.46 (1H, br s), 1.60-2.00 (6H, m), 2.53-2.70 (3H, m), 3.76 (2H, t, J= 6.4Hz), 7.83 (1H, d, J= 9.2Hz), 8.29 (1H, d, J= 9.2Hz), 8.51 (1H, s).

#### 30     **Reference Example 230**

To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.50 g), 2-methylthio-5-(trifluoromethyl)pyrimidine (1.40 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.48 g) at 0°C,  
35 and, after termination of hydrogen generation, the mixture was

stirred at room temperature for 4 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture  
5 of the obtained residue, conc. hydrochloric acid (3 drops) and methanol (50 ml) was refluxed for 4 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and  
10 concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-(1-methylethyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}-1-propanol (240 mg, 11%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-chloroform (1:3, volume  
15 ratio). melting point: 98-99°C.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.38 (6H, d, J= 7.0Hz), 1.85-2.01 (2H, m), 2.63 (2H, t, J= 7.7Hz), 3.11 (1H, septet, J= 7.0Hz), 3.77 (2H, t, J= 6.2Hz), 8.34 (1H, s), 8.91 (2H, s).

#### Reference Example 231

20 To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.00 g), 2-methylthiopyrimidine-5-carbonitrile (0.80 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.24 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at  
25 room temperature for 2 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the obtained residue, conc. hydrochloric acid (3 drops) and  
30 methanol (20 ml) was refluxed for 4 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column  
35 chromatography, and 2-[4-(3-hydroxypropyl)-3-(1-methylethyl)-

1H-pyrazol-1-yl]pyrimidine-5-carbonitrile (450 mg, 36%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-chloroform (1:4, volume ratio). melting point: 153-154°C.

5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.38 (6H, d, J= 7.0Hz), 1.44 (1H, t, J= 5.2Hz), 1.84-2.00 (2H, m), 2.62 (2H, t, J= 7.8Hz), 3.10 (1H, septet, J= 7.0Hz), 3.77 (2H, q, J= 5.9Hz), 8.31 (1H, s), 8.93 (2H, s).

【0182】

#### 10 **Reference Example 232**

To a mixture of 4-[3-(methoxymethoxy)propyl]-3-(1-methylethyl)-1H-pyrazole (1.20 g), 2-chloro-5-ethylpyrimidine (0.89 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.29 g) at 0°C, and, after termination of  
15 hydrogen generation, the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the  
20 obtained residue, conc. hydrochloric acid (1 ml) and methanol (20 ml) was refluxed for 5 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue  
25 was subjected to silica gel column chromatography, and 3-[1-(5-ethylpyrimidin-2-yl)-3-(1-methylethyl)-1H-pyrazol-4-yl]-1-propanol (1.36 g, 88%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (7:3, volume ratio). melting point: 70-71°C.

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.27 (3H, t, J= 7.5Hz), 1.37 (6H, d, J= 6.8Hz), 1.73 (1H, br s), 1.83-2.00 (2H, m), 2.54-2.72 (4H, m), 3.11 (1H, septet, J= 7.0Hz), 3.75 (2H, t, J= 6.4Hz), 8.28 (1H, s), 8.53 (2H, s).

#### **Reference Example 233**

35 To a mixture of 3-(1-ethylpropyl)-4-[3-

(methoxymethoxy)propyl]-1H-pyrazole (2.70 g), 2-methylthio-5-(trifluoromethyl)pyrimidine (2.62 g) and tetrahydrofuran (50 ml) was added sodium hydride (60%, in oil, 0.58 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at room temperature overnight. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the obtained residue, conc. hydrochloric acid (3 drops) and methanol (50 ml) was refluxed for 6 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}-1-propanol (1.19 g, 31%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 0.87 (6H, t, J= 7.3Hz), 1.63-2.00 (6H, m), 2.55-2.80 (3H, m), 3.76 (2H, t, J= 6.2Hz), 8.35 (1H, s), 8.92 (2H, s).

#### Reference Example 234

A mixture of methyl (2-hydroxy-3-methoxyphenyl)acetate (1.00 g), benzyl alcohol (1.10 g), p-toluenesulfonic acid-monohydrate (0.10 g) and toluene (15 ml) was stirred overnight at 90°C while evaporating produced methanol. The reaction mixture was concentrated. The residue was subjected to silica gel column chromatography, and benzyl (2-hydroxy-3-methoxyphenyl)acetate (1.35 g, 97%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.73 (2H, s), 3.88 (3H, s), 5.16 (2H, s), 5.87 (1H, s), 6.80 (3H, s), 7.28-7.40 (5H, m).

【0183】

#### Reference Example 235

A mixture of ethyl 3-[3-(1-ethylpropyl)-1H-pyrazol-4-yl]propanoate (10.57 g), benzyl bromide (4.40 ml), potassium carbonate (5.00 g) and N,N-dimethylformamide (80 ml) was stirred at 70°C for 6 hours. The reaction mixture was poured  
5 into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with  
10 ethyl acetate-hexane (1:4, volume ratio). To a mixture of lithium aluminum hydride (1.50 g) and tetrahydrofuran (20 ml) was slowly added a solution of the above-mentioned oily substance in tetrahydrofuran (10 ml) at 0°C, and the mixture was stirred at room temperature for 30 minutes. Acetone (10  
15 ml) was slowly added to decompose excess lithium aluminum hydride, and brine (4 ml) was further added. The precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and 3-[1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-5-yl]-1-propanol  
20 (7.69 g, yield 80%) was obtained as a colorless oil from a fraction eluted with acetone-hexane (1:2, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.83 (6H, t, J= 7.3Hz), 1.35 (1H, t, J= 5.4Hz), 1.60-1.85 (6H, m), 2.48 (2H, t, J= 7.8Hz), 3.67 (2H, q, J= 5.9Hz), 5.24 (2H, s), 7.03-7.40 (6H, m).

25 **Reference Example 236**

To a mixture of 3-[1-benzyl-3-(1-ethylpropyl)-1H-pyrazol-5-yl]-1-propanol (7.53 g), N-ethyldiisopropylamine (11.5 ml) and tetrahydrofuran (100 ml) was added chloromethyl methyl  
ether (6.40 ml) at 0°C and the mixture was stirred at room  
30 temperature overnight. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless  
35 oil was obtained from a fraction eluted with ethyl acetate-

hexane (1:2, volume ratio). A mixture of the obtained oily substance, 5% palladium-carbon (0.8 g) and tetrahydrofuran (50 ml) was stirred overnight at 50°C under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate  
5 was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with acetone-hexane (2:3, volume ratio). 3-(1-Ethylpropyl)-4-[3-(methoxymethoxy)propyl]-1H-pyrazole (4.93 g, 77%) was obtained as a colorless oil.  
10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.82 (6H, d, J = 7.3 Hz), 1.50-1.94 (6H, m), 2.44-2.70 (3H, m), 3.38 (3H, s), 3.57 (2H, t, J = 6.4 Hz), 4.64 (2H, s), 7.36 (1H, s).

#### Reference Example 237

A mixture of 3-ethylsalicylaldehyde (8.10 g), benzyl  
15 bromide (11.07 g), potassium carbonate (8.94 g) and N,N-dimethylformamide (30 ml) was stirred at 50°C for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
20 (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 2-benzyloxy-3-ethylbenzaldehyde (12.50 g, yield 96%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (2:98, volume ratio).  
25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.27 (3H, t, J = 7.6 Hz), 2.76 (2H, q, J = 7.6 Hz), 4.98 (2H, s), 7.22 (1H, t, J = 7.6 Hz), 7.39-7.43 (5H, m), 7.51-7.53 (1H, m), 7.70-7.72 (1H, m), 10.28 (1H, m).

【0184】

#### Reference Example 238

A mixture of ethyl 3-(3-ethoxy-1H-pyrazol-4-yl)propanoate  
30 (7.01 g), sodium hydride (60%, in oil, 1.59 g) and N,N-dimethylformamide (165 ml) was stirred at room temperature for 30 minutes. 2-Chloro-4-(trifluoromethyl)pyridine (6.00 g) was added and the mixture was stirred overnight. Saturated aqueous  
35 ammonium chloride solution was added to the reaction mixture,

and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-ethoxy-1-[4-

5 (trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propanoate (9.05 g, yield 77%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.26 (3H, t, J = 7.0 Hz), 1.44 (3H, t, J = 7.0  
10 Hz), 2.56 - 2.66 (2H, m), 2.70 - 2.81 (2H, m), 4.15 (2H, q, J = 7.0 Hz), 4.37 (2H, q, J = 7.0 Hz), 7.18 - 7.24 (1H, m), 7.91 - 7.94 (1H, m), 8.18 (1H, s), 8.45 (1H, d, J = 5.0 H).

#### Reference Example 239

To a solution of ethyl 3-{3-ethoxy-1-[4-  
15 (trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propanoate (10.2 g) in tetrahydrofuran (280 ml) was dropwise added a 0.93 M solution (92.0 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. 1N Hydrochloric acid was added to the reaction mixture  
20 and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated to give 3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (9.07 g, quantitative) as a white solid. The crystals were  
25 recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 73-74°C.

#### Reference Example 240

A mixture of ethyl 3-isopropyl-1H-pyrazole-4-carboxylate (12.8 g), sodium hydride (60%, in oil, 3.08 g) and N,N-  
30 dimethylformamide (350 ml) was stirred at room temperature for 30 minutes. 2,5-Dichloropyridine (11.4 g) was added and the mixture was stirred overnight at 100°C. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was  
35 washed with saturated aqueous sodium chloride solution and

saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio). To a solution of the obtained solid in tetrahydrofuran (230 ml) was dropwise added a 1.0 M solution (176 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. Dilute hydrochloric acid was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and [1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]methanol (12.6 g, yield 71%) was obtained as a white solid from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 135-136°C.

【0185】

#### Reference Example 241

A mixture of ethyl (E)-3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propenoate (1.35 g), platinum oxide (100 mg) and ethanol (100 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Platinum oxide was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propanoate (1.09 g, yield 68%) was obtained as a white solid from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 70-71°C.

#### Reference Example 242

To a solution of ethyl 3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propanoate (1.08 g) in tetrahydrofuran (30 ml) was dropwise added a 0.93 M a solution



(9.8 ml) of diisobutylaluminum hydride in hexane at 0°C, and the mixture was stirred at room temperature for 1 hour. 1N Hydrochloric acid was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was  
5 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated to give 3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (0.92 g, quantitative) as a white solid. The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 93-  
10 95°C.

#### Reference Example 243

Diethyl ethoxymethylenemalonate (56.9 ml) was added to a solution of ethylhydrazine oxalate (42.6 g) in toluene (150 ml)-acetic acid (150 ml)-water (100 ml) and the mixture was  
15 stirred at room temperature for 1 hour, and at 100°C overnight. The reaction solution was cooled to room temperature, the organic solvent was evaporated under reduced pressure, and the residue was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride  
20 solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was washed with diisopropyl ether to give a pale-yellow solid. A mixture of the obtained solid, benzyl bromide (29.0 ml), potassium carbonate (33.7 g) and N,N-dimethylformamide (350 ml) was stirred at room temperature for 2.5 days and saturated  
25 aqueous ammonium chloride solution was added to the reaction mixture. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl  
30 3-benzyloxy-1-ethyl-1H-pyrazole-4-carboxylate (34.0 g, yield 43%) was obtained as a pale yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.33 (3H, t, J = 7.4 Hz), 1.46 (3H, t, J = 7.4 Hz), 4.01 (2H, q, J = 7.4 Hz), 4.27 (2H, q, J = 7.4 Hz), 7.22  
35 - 7.42 (3H, m), 7.46 - 7.54 (2H, m), 7.72 (1H, s).

【0186】

#### Reference Example 244

To a mixture of ethyl 3-benzyloxy-1-ethyl-1*H*-pyrazole-4-carboxylate (34.0 g) and tetrahydrofuran (500 ml) was slowly  
5 added lithium aluminum hydride (4.70 g) at 0°C and the mixture was stirred at room temperature for 1.5 hours. 1*N* Hydrochloric acid was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and  
10 concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-1-ethyl-1*H*-pyrazol-4-yl)methanol (19.9 g, yield 69%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (3:2, volume ratio).

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.42 (3H, t, *J* = 7.2 Hz), 3.98 (2H, d, *J* = 7.2 Hz), 4.47 (2H, s), 5.24 (2H, s), 7.20 (1H, s), 7.27 - 7.39 (3H, m), 7.40 - 7.46 (2H, m).

#### Reference Example 245

To a mixture of (3-benzyloxy-1-ethyl-1*H*-pyrazol-4-yl)methanol (1.40 g), acetone cyanohydrin (1.10 ml),  
20 tributylphosphine (3.00 ml) and tetrahydrofuran (60 ml) was added 1,1'-azodicarbonyldipiperidine (3.04 g) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected  
25 to silica gel column chromatography, and (3-benzyloxy-1-ethyl-1*H*-pyrazol-4-yl)acetonitrile (0.72 g, yield 49%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio).

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.44 (3H, t, *J* = 7.2 Hz), 3.43 (2H, s), 3.99 (2H, q, *J* = 7.2 Hz), 5.22 (2H, s), 7.23 - 7.46 (6H, m).

#### Reference Example 246

A mixture of (3-benzyloxy-1-ethyl-1*H*-pyrazol-4-yl)acetonitrile (720 mg), 6*N* aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was  
35 stirred under reflux for 2 days. After cooling, the reaction

mixture was acidified by adding 1N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the residue, a 10%  
5 solution (30 ml) of hydrochloric acid in methanol and methanol (30 ml) was stirred at room temperature for 2.5 hours. After concentration, the residue was subjected to silica gel column chromatography, and methyl (3-benzyloxy-1-ethyl-1H-pyrazol-4-yl)acetate (470 mg, yield 57%) was obtained as a yellow oily  
10 substance from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.43 (3H, t, J = 7.2 Hz), 3.40 (2H, s), 3.68 (3H, s), 3.98 (2H, q, J = 7.2 Hz), 5.22 (2H, s), 7.23 (1H, s), 7.27 - 7.39 (3H, m), 7.40 - 7.47 (2H, m).

15    **[0187]**

#### **Reference Example 247**

A mixture of methyl (3-benzyloxy-1-ethyl-1H-pyrazol-4-yl)acetate (11.0 g), 5% palladium-carbon (2.19 g) and ethanol (300 ml) was stirred overnight at room temperature under a  
20 hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (1-ethyl-3-hydroxy-1H-pyrazol-4-yl)acetate (7.17 g, yield 97%) was obtained as a white solid from a fraction eluted with  
25 ethyl acetate. The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 72-73°C.

#### **Reference Example 248**

To a solution of cyclohexylhydrazine hydrochloride (30.0  
30 g) in toluene (100 ml)-acetic acid (100 ml) was added sodium acetate (16.3 g) and the mixture was reacted at room temperature for 10 minutes. A solution of diethyl ethoxymethylenemalononate (39.8 ml) was added and the mixture was stirred overnight at 80°C. After cooling the reaction  
35 solution to room temperature, the resulting precipitate was

removed by filtration. The filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 1-cyclohexyl-3-hydroxy-1*H*-pyrazole-4-carboxylate (46.2 g, yield 97%) was obtained as a purple solid from a fraction  
5 eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 91-92°C.

#### Reference Example 249

A mixture of ethyl 1-cyclohexyl-3-hydroxy-1*H*-pyrazole-4-  
10 carboxylate (46.0 g), benzyl bromide (24.1 ml), potassium carbonate (28.1 g) and *N,N*-dimethylformamide (400 ml) was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and extracted with ethyl acetate. The ethyl acetate layer was  
15 washed with saturated aqueous ammonia chloride solution and saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-benzyloxy-1-cyclohexyl-1*H*-pyrazole-4-carboxylate (61.5 g, yield 97%) was obtained as a  
20 yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.10 - 1.28 (3H, m), 1.37 (3H, t, J = 7.2 Hz), 1.38 - 1.49 (2H, m), 1.56 - 1.82 (5H, m), 3.81 - 3.92 (1H, m), 4.31 (2H, q, J = 7.2 Hz), 5.41 (2H, s), 7.32 - 7.39 (5H, m),  
25 7.77 (1H, s).

【0188】

#### Reference Example 250

To a mixture of ethyl 3-benzyloxy-1-cyclohexyl-1*H*-pyrazole-4-carboxylate (31.5 g) and tetrahydrofuran (300 ml)  
30 was slowly added lithium aluminum hydride (2.73 g) at 0°C and the mixture was stirred at room temperature for 1.5 hours. Aluminum lithium hydride (1.81 g) was added, and the mixture was stirred at room temperature for 1 hour. 1*N* Hydrochloric acid was added to the reaction mixture, and extracted with  
35 ethyl acetate. The ethyl acetate layer was washed with 1*N*

hydrochloric acid and saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)methanol (16.5 g, yield 5 60%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.14 - 1.35 (3H, m), 1.40 - 1.86 (1H, brm), 1.59 - 1.86 (7H, m), 3.87 - 4.00 (1H, m), 4.48 (2H, d, J = 4.5 Hz), 5.24 (2H, s), 7.31 - 7.41 (6H, m).

#### 10 Reference Example 251

To a mixture of (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)methanol (16.5 g), acetone cyanohydrin (8.77 ml), tributylphosphine (21.5 ml) and tetrahydrofuran (350 ml) was added a 40% solution (39.1 ml) of diethyl azodicarboxylate in 15 toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and diisopropyl ether was added to the residue. The resulting unnecessary material was removed by filtration. The filtrate was concentrated. The residue was subjected to silica gel 20 column chromatography, and a pale yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 6N aqueous sodium hydroxide solution (100 ml), tetrahydrofuran (100 ml) and ethanol (100 ml) was stirred under reflux for one 25 day. After cooling to room temperature, the reaction solution was concentrated. The residue was diluted with water (300 ml) and washed with ethyl acetate. The aqueous layer was acidified by adding conc. hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated 30 aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated to give (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)acetic acid (7.86 g, yield 44%) as a yellow oily substance. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.14 - 1.28 (3H, m), 1.54 - 1.84 (7H, m), 3.40 (2H, s), 3.76 - 3.92 (1H, m), 5.05 (2H, s), 7.32 - 7.41 (6H, 35 m).

#### Reference Example 252

A mixture of (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)acetic acid (7.86 g), a 10% solution (125 ml) of hydrochloric acid in methanol and methanol (125 ml) was stirred overnight at room temperature. The reaction solution was concentrated and the residue was diluted with ethyl acetate. The diluted solution was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)acetate (1.98 g, yield 24%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.12 - 1.30 (3H, m), 1.52 - 1.84 (7H, m), 3.38 (2H, s), 3.70 (3H, s), 3.76 - 3.89 (1H, m), 5.06 (2H, s), 7.33 - 7.42 (6H, m).

[0189]

#### Reference Example 253

A mixture of methyl (3-benzyloxy-1-cyclohexyl-1*H*-pyrazol-4-yl)acetate (1.98 g), 5% palladium-carbon (400 mg) and ethanol (60 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (1-cyclohexyl-3-hydroxy-1*H*-pyrazol-4-yl)acetate (1.24 g, yield 92%) was obtained as a white solid from a fraction eluted with ethyl acetate-hexane (3:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 135-136°C.

#### Reference Example 254

To a solution of diethyl 2-formylsuccinate (2.02 g) in ethanol (15 ml) was dropwise added a solution of methylhydrazine (580 μL) in ethanol (5 ml) at 0°C. The reaction solution was stirred at 0°C for 30 minutes and at room temperature for 1 hour, followed by heating to 80°C. After

stirring at said temperature overnight, the reaction solution was concentrated. The obtained brown solid was recrystallized from ethyl acetate-hexane to give ethyl (5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)acetate (1.42 g, yield 77%) as colorless  
5 crystals. melting point: 104-105°C.

#### Reference Example 255

To a solution of ethylhydrazine oxalate (4.08 g) in ethanol (30 ml) was added sodium ethoxide (3.70 g) at 0°C. The mixture was stirred at room temperature for 1 hour and a  
10 solution of diethyl 2-formylsuccinate (5.00 g) in ethanol (30 ml) was dropwise added at 0°C. The reaction solution was stirred at 0°C for 30 minutes and at room temperature for 2 hours, which was followed by heating until reflux. After stirring at said temperature overnight, the reaction solution  
15 was cooled to room temperature, and the resulting precipitate was removed by filtration. The filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and ethyl (1-ethyl-5-hydroxy-1*H*-pyrazol-4-yl)acetate (2.36 g, yield 48%) was obtained as a brown solid  
20 from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 107-108°C.

[0190]

#### Reference Example 256

25 To a solution of ethyl hydrazinoacetate hydrochloride (3.56 g) in ethanol (25 ml) was added 1*N* aqueous sodium hydroxide solution (23.1 ml) at 0°C. The reaction solution was stirred at room temperature for 1 hour and a solution of ethyl 2-formylpropanoate (3.00 g) in ethanol (75 ml) was dropwise  
30 added at 0°C. The reaction solution was stirred at room temperature for 1 hour, which was followed by heating until reflux. After stirring overnight, the reaction solution was cooled to room temperature, and concentrated. The obtained residue was subjected to silica gel column chromatography, and  
35 ethyl (5-hydroxy-4-methyl-1*H*-pyrazol-1-yl)acetate (3.35 g,

yield 79%) was obtained as a colorless oil from a fraction eluted with methanol-ethyl acetate (1:7, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.25 - 1.32 (3H, m), 1.39 (1.0H, d, J = 8.1 Hz), 1.89 (2H, s), 3.22 (0.3H, t, J = 8.1 Hz), 4.17 - 4.26  
5 (2H, m), 4.45 (0.6H, s), 4.58 (1.4H, s), 7.22 - 7.24 (0.7H, m), 7.29 - 7.31 (0.3H, m).

#### Reference Example 257

To a solution of ethyl hydrazinoacetate hydrochloride (1.64 g) in ethanol (10 ml) was dropwise added 1N aqueous  
10 sodium hydroxide solution (10.6 ml) at 0°C. The reaction solution was stirred at room temperature for 1 hour and a solution of ethyl 2-formylbutanoate (2.13 g) in ethanol (30 ml) was dropwise added at 0°C. The reaction solution was stirred at room temperature for 2.5 hours, and at 80°C  
15 overnight. The reaction solution was cooled to room temperature and concentrated. The obtained residue was subjected to silica gel column chromatography, and ethyl (4-ethyl-5-hydroxy-1H-pyrazol-1-yl)acetate (1.54 g, yield 81%) was obtained as a white solid from a fraction eluted with  
20 ethyl acetate-hexane (19:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane to give colorless crystals. melting point: 77-78°C.

#### Reference Example 258

A mixture of ethyl (E)-3-(1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl)propenoate (30.25 g), 5% palladium-carbon (3.5 g) and tetrahydrofuran (200 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and  
30 ethyl 3-[1-benzyl-3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (11.73 g, yield 39%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.20 (3H, t, J= 7.2Hz), 1.30 (6H, d, J= 7.0Hz), 2.44-2.55 (2H, m), 2.68-2.79 (2H, m), 2.99 (1H,  
35



septet,  $J = 7.0\text{Hz}$ ), 4.09 (2H, q,  $J = 7.2\text{Hz}$ ), 5.23 (1H, s), 7.12-7.40 (6H, m).

【0191】

#### Reference Example 259

5 Ethyl 3-[3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (10.06 g, yield 47%) was obtained as a yellow oily substance from a fraction eluted following the compound described in Reference Example 258 in the silica gel column chromatography described in Reference Example 258.

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.25 (3H, t,  $J = 7.2\text{Hz}$ ), 1.29 (6H, d,  $J = 7.0\text{Hz}$ ), 2.50-2.60 (2H, m), 2.72-2.83 (2H, m), 3.06 (1H, septet,  $J = 7.0\text{Hz}$ ), 4.14 (2H, q,  $J = 7.2\text{Hz}$ ), 7.34 (1H, s).

#### Reference Example 260

To a mixture of 2-benzyloxy-3-ethylbenzaldehyde (12.40 g), methyl (methylthio)methyl sulfoxide (12.82 g) and 15 tetrahydrofuran (100 ml) was added a 40% solution (2.00 ml) of benzyltrimethylammonium hydroxide in methanol at room temperature, and the mixture was stirred at  $65^\circ\text{C}$  for 2 hours. The reaction solution was concentrated. The residue was 20 subjected to silica gel column chromatography, and 2-(2-benzyloxy-3-ethylphenyl)-1-(methylsulfanyl)ethenyl methyl sulfoxide (15.20 g, yield 85%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.24 (3H, t,  $J = 7.6\text{ Hz}$ ), 2.29 (3H, s), 2.72 (2H, q,  $J = 7.6\text{ Hz}$ ), 2.72 (3H, s), 4.79-4.82 (2H, m), 7.16 (1H, t,  $J = 7.6\text{ Hz}$ ), 7.29 (1H, dd,  $J = 7.6, 1.6\text{Hz}$ ), 7.32-7.42 (3H, m), 7.49-7.51 (2H, m), 7.95 (1H, dd,  $J = 7.6, 1.6\text{Hz}$ ), 8.03 (1H, s).

#### Reference Example 261

30 A mixture of 2-(2-benzyloxy-3-ethylphenyl)-1-(methylsulfanyl)ethenyl methyl sulfoxide (14.90 g), a 10% solution (100 ml) of hydrogen chloride in methanol and methanol (100 ml) was refluxed for 16 hours. The reaction solution was concentrated. Ethyl acetate and aqueous sodium 35 hydrogen carbonate were added to the residue and the mixture

extracted. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-benzyloxy-3-ethylphenyl)acetate  
5 (9.60 g, yield 79%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (4:96, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.25 (3H, t,  $J=7.6$  Hz), 2.73 (2H, q,  $J=7.6$  Hz), 3.66 (3H, s), 3.69 (2H, s), 4.84 (2H, s), 7.08 (1H, t,  
10  $J=7.6$  Hz), 7.13 (1H, dd,  $J=7.6, 1.6\text{Hz}$ ), 7.19 (1H, dd,  $J=7.6, 1.6\text{Hz}$ ), 7.32-7.43 (3H, m), 7.46-7.48 (2H, m).

【0192】

#### Reference Example 262

A mixture of methyl (2-benzyloxy-3-ethylphenyl)acetate  
15 (9.20 g), 5% palladium-carbon (1.00 g) and methanol (50 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-ethyl-2-  
20 hydroxyphenyl)acetate (5.40 g, yield 86%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.23 (3H, t,  $J=7.6$  Hz), 2.69 (2H, q,  $J=7.6$  Hz), 3.68 (2H, s), 3.75 (3H, s), 6.83 (1H, t,  $J=7.6$  Hz), 6.94  
25 (1H, dd,  $J=7.6, 1.6\text{Hz}$ ), 7.10 (1H, dd,  $J=7.6, 1.2\text{Hz}$ ), 7.53 (1H, s).

#### Reference Example 263

A mixture of 2-coumaranone (25.00 g), a 10% solution (30 ml) of hydrogen chloride in methanol and methanol (30 ml) was  
30 stirred at  $50^\circ\text{C}$  for 30 minutes. The reaction solution was concentrated. Ethyl acetate and aqueous sodium hydrogen carbonate were added to the residue and the mixture was extracted. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and  
35 concentrated. The residue was subjected to silica gel column

chromatography, and methyl (2-hydroxyphenyl)acetate (30.60 g, yield 99%) was obtained as a colorless oil from a fraction eluted with diethyl ether.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.68 (2H, s), 3.74 (3H, s), 6.86-6.93 (2H, m),  
5 7.10 (1H, dd, J=7.2,1.6 Hz), 7.16-7.20 (1H, m), 7.35 (1H, brs).

#### Reference Example 264

To a mixture of methyl (2-hydroxyphenyl)acetate (4.99 g), diisopropylamine (610 mg) and methylene chloride (300 ml) was  
10 slowly added N-bromosuccinimide (5.34 g) under ice-cooling, and the mixture was stirred for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and  
15 concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-bromo-2-hydroxyphenyl)acetate (5.60 g, yield 76%) was obtained as a colorless oil from a fraction eluted with chloroform.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.71 (2H, s), 3.73 (3H, s), 6.32 (1H, s), 6.78  
20 (1H, t, J=8.0 Hz), 7.11 (1H, dt, J=8.0,0.8Hz), 7.41 (1H, dd, J=8.0,1.6 Hz).

【0193】

#### Reference Example 265

A mixture of methyl (3-bromo-2-hydroxyphenyl)acetate  
25 (4.30 g), benzyl bromide (3.30 g), potassium carbonate (4.84 g) and acetone (50 ml) 1 hour was refluxed. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-benzyloxy-3-bromophenyl)acetate (4.10 g, yield 70%) was obtained as a  
30 colorless oil from a fraction eluted with ethyl acetate-hexane (4:96, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.65 (3H, s), 3.66 (2H, s), 5.01 (2H, s), 7.00 (1H, t, J=8.0 Hz), 7.23 (1H, dd, J=8.0,1.2 Hz), 7.33-7.43 (3H, m), 7.49-7.54 (3H, m).

#### 35 Reference Example 266

A mixture of methyl (2-benzyloxy-3-bromophenyl)acetate (2.01 g), copper(I) cyanide (2.14 g) and N,N-dimethylformamide (30 ml) was stirred at 190°C for 16 hours. The reaction mixture was poured into a mixture of iron(III) chloride and dilute hydrochloric acid. The mixture was stirred for 1 hour and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-benzyloxy-3-cyanophenyl)acetate (1.20 g, yield 71%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.62 (2H, s), 3.64 (3H, s), 5.24 (2H, s), 7.16 (1H, t, J=7.6 Hz), 7.34-7.42 (3H, m), 7.46-7.50 (3H, m), 7.57 (1H, dd, J=7.6, 1.6 Hz).

#### Reference Example 267

A mixture of methyl (2-benzyloxy-3-cyanophenyl)acetate (1.10 g), 5% palladium-carbon (110 mg) and methanol (15 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-cyano-2-hydroxyphenyl)acetate (700 mg, yield 94%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.73 (2H, s), 3.80 (3H, s), 6.95 (1H, t, J=7.6 Hz), 7.31 (1H, dt, J=7.6, 0.8 Hz), 7.48 (1H, dd, J=7.6, 1.6 Hz).

[0194]

#### Reference Example 268

A mixture of methyl (2-benzyloxy-3-bromophenyl)acetate (1.90 g), copper(I) chloride (2.24 g) and N,N-dimethylformamide (20 ml) was stirred at 190°C for 16 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-benzyloxy-3-chlorophenyl)acetate (740 mg, yield 45%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (2:98, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.64 (2H, s), 3.65 (3H, s), 5.02 (2H, s), 7.05 (1H, t, J=8.0 Hz), 7.17 (1H, dd, J=8.0,1.6 Hz), 7.34-7.42 (4H, m), 7.46-7.51 (2H, m).

#### Reference Example 269

A mixture of methyl (2-benzyloxy-3-chlorophenyl)acetate (680 mg), 5% palladium-carbon (70 mg) and methanol (15 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and methyl (3-chloro-2-hydroxyphenyl)acetate (300 mg, yield 64%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 3.70 (2H, s), 3.73 (3H, s), 6.28 (1H, s), 6.84 (1H, t, J=8.0 Hz), 7.08 (1H, dd, J=8.0,0.8 Hz), 7.27 (1H, dd, J=8.0,1.0 Hz).

#### Reference Example 270

To a mixture of ethyl 3-[3-(1-methylethyl)-1H-pyrazol-4-yl]propanoate (1.50 g), 2-chloro-5-(trifluoromethyl)-1,3,4-thiadiazole (1.50 g) and N,N-dimethylformamide (15 ml) was added sodium hydride (60%, in oil, 0.34 g) at 0°C, and, after termination of hydrogen generation, the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-{3-(1-methylethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-1H-pyrazol-4-yl}propanoate (1.29 g, 50%) was obtained as a yellow oily substance from a fraction eluted with ethyl

acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.27 (3H, t, J= 7.1Hz), 1.30 (6H, d, J= 7.0Hz), 2.57-2.90 (4H, m), 3.01 (1H, septet, J= 7.0Hz), 4.17 (2H, q, J= 7.1Hz), 8.13 (1H, s).

**5 Reference Example 271**

To a solution of ethyl 3-{3-(1-methylethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-1H-pyrazol-4-yl}propanoate (1.29 g) in tetrahydrofuran (15 ml) was dropwise added a 1.5M solution (5.7 ml) of diisobutylaluminum hydride  
10 in toluene at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The  
15 residue was subjected to silica gel column chromatography, and 3-{3-(1-methylethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-1H-pyrazol-4-yl}-1-propanol (0.82 g, yield 73%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). The crystals were  
20 recrystallized from ethyl acetate-hexane. melting point: 89-90°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.30 (6H, d, J= 7.0Hz), 1.45 (1H, br s), 1.82-1.98 (2H, m), 2.62 (2H, t, J= 7.8Hz), 3.00 (1H, septet, J= 7.0Hz), 3.76 (2H, t, J= 6.0Hz), 8.13 (1H, s).

**25 Reference Example 272**

To a mixture of 1-benzyl-4-[3-(1,3-dioxolan-2-yl)propyl]-1H-pyrazol-3-ol (21.8 g) and N,N-dimethylformamide (150 ml) potassium carbonate (16.7 g) was added diethylsulfuric acid (17.3 ml) at room temperature, and the mixture was stirred  
30 overnight. Saturated aqueous ammonia chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained residue was subjected to silica gel  
35 column chromatography, and 1-benzyl-4-[3-(1,3-dioxolan-2-

yl)propyl]-3-ethoxy-1H-pyrazole (19.5 g, yield 82%) was obtained as a yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.36 (3H, t, J = 6.9 Hz), 1.57 - 1.74 (4H, m), 2.32 - 2.39 (2H, m), 3.80 - 3.98 (4H, m), 4.22 (2H, q, J = 6.9 Hz), 4.82 - 4.87 (1H, m), 5.07 (2H, s), 6.93 (1H, s), 7.13 - 7.17 (2H, m), 7.23 - 7.35 (3H, m).

[0195]

#### Example 1

A mixture of 3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-propyl methanesulfonate (1.04 g), sodium iodide (450 mg), methyl 4-hydroxyphenylacetate (500 mg), potassium carbonate (440 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [4-(3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}propoxy)phenyl]acetic acid (300 mg, yield 25%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 127-128°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.18-2.32 (2H, m), 2.98-3.10 (2H, m), 3.60 (2H, s), 3.98-4.08 (2H, m), 6.37 (1H, s), 6.82-6.90 (2H, m), 7.15-7.24 (2H, m), 7.66-7.75 (2H, m), 7.86-7.94 (2H, m).

#### Example 2

A mixture of 3-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)-1-propyl methanesulfonate (1.04 g), sodium iodide (450 mg), methyl 4-hydroxybenzoate (460 mg), potassium carbonate (450 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 4-(3-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)propoxy)benzoic acid (840 mg, yield 72%). The crystals were recrystallized from acetone-hexane. melting point: 221-222°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.20-2.38 (2H, m), 3.00-3.14 (2H, m), 4.05-4.18 (2H, m), 6.39 (1H, s), 6.86-6.96 (2H, m), 7.64-7.74 (2H, m), 7.86-8.08 (4H, m).

### Example 3

A mixture of 3-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)-1-propyl methanesulfonate (1.04 g), sodium iodide (450 mg), methyl 3-hydroxyphenylacetate (500 mg), potassium carbonate (450 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column



chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol  
5 (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
10 collected by filtration to give [3-(3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}propoxy)phenyl]acetic acid (630 mg, yield 52%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 126-127°C.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.16-2.34 (2H, m), 2.98-3.12 (2H, m), 3.63  
15 (2H, s), 4.00-4.10 (2H, m), 6.38 (1H, s), 6.76-6.94 (3H, m), 7.18-7.32 (1H, m), 7.66-7.75 (2H, m), 7.86-7.96 (2H, m).

[0196]

#### Example 4

A mixture of 3-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)-1-propyl methanesulfonate (1.04 g), sodium iodide  
20 (520 mg), methyl 3-hydroxybenzoate (460 mg), potassium carbonate (450 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl  
25 acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
30 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was  
35 washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}propoxy)benzoic acid (860 mg, yield 74%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 133-134°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.20-2.37 (2H, m), 3.02-3.14 (2H, m), 4.06-4.17 (2H, m), 6.39 (1H, s), 7.10-7.20 (1H, m), 7.34-7.44 (1H, m), 7.58-7.76 (4H, m), 7.86-7.96 (2H, m).

#### Example 5

A mixture of 3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-propyl methanesulfonate (1.04 g), sodium iodide (520 mg), ethyl 3-(4-hydroxyphenyl)propionate (600 mg), potassium carbonate (450 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}propoxy)phenyl]propionic acid (520 mg, yield 42%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 174-175°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.16-2.34 (2H, m), 2.59-2.72 (2H, m), 2.84-3.12 (4H, m), 3.98-4.08 (2H, m), 6.37 (1H, s), 6.78-6.88 (2H, m), 7.07-7.18 (2H, m), 7.66-7.76 (2H, m), 7.86-7.96 (2H, m).

#### Example 6

A mixture of 3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-propyl methanesulfonate (1.04 g), sodium iodide (500 mg), methyl salicylate (460 mg), potassium carbonate (500 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-(3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}propoxy)benzoic acid (710 mg, yield 61%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 132-133°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.34-2.52 (2H, m), 3.03-3.16 (2H, m), 4.18-4.42 (2H, m), 6.43 (1H, s), 7.00-7.24 (2H, m), 7.50-7.64 (1H, m), 7.65-7.76 (2H, m), 7.85-7.96 (2H, m), 8.16-8.24 (1H, m).

25    **[0197]**

#### **Example 7**

A mixture of 3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-propyl methanesulfonate (1.04 g), sodium iodide (500 mg), methyl 3-hydroxy-1-methyl-1H-pyrazole-5-carboxylate (470 mg), potassium carbonate (500 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica

gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and  
5 methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected  
10 by filtration to give 1-methyl-3-(3-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)propoxy)-1H-pyrazole-5-carboxylic acid (870 mg, yield 74%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 162-163°C.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.16-2.34 (2H, m), 2.96-3.10 (2H, m), 4.04 (3H, s), 4.17-4.28 (2H, m), 6.30 (1H, s), 6.39 (1H, s), 7.67-7.77 (2H, m), 7.87-7.97 (2H, m).

#### Example 8

A mixture of 3-(3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)-1-propyl methanesulfonate (1.04 g), sodium iodide  
20 (500 mg), methyl 3-hydroxy-1-phenyl-1H-pyrazole-5-carboxylate (650 mg), potassium carbonate (500 mg) and N,N-dimethylformamide (10 ml) was stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and  
25 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume  
30 ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added, and extracted with ethyl acetate. The ethyl acetate layer was washed with  
35 saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and

concentrated. The obtained colorless crystals were collected by filtration to give 1-phenyl-3-(3-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}propoxy)-1H-pyrazole-5-carboxylic acid (1.16 g, yield 85%). The crystals were  
5 recrystallized from ethyl acetate-hexane. melting point: 145-146°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.16-2.36 (2H, m), 2.96-3.10 (2H, m), 4.24-4.36 (2H, m), 6.40 (1H, s), 6.50 (1H, s), 7.36-7.47 (5H, m), 7.65-7.75 (2H, m), 7.84-7.94 (2H, m).

#### 10 **Example 9**

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (500 mg), methyl 3-(4-hydroxyphenyl)propionate (370 mg), triphenylphosphine (530 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution  
15 of diethyl azodicarboxylate in toluene (900 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane  
20 (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (3 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (3 ml) was added and extracted with ethyl acetate. The ethyl acetate layer was washed with  
25 saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(4-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxy)phenyl)propionic acid (620 mg, yield 79%). The crystals were recrystallized from ethyl  
30 acetate-hexane. melting point: 195-196°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.39 (3H, s), 4.64 (2H, s), 4.94 (2H, s), 6.87-6.97 (4H, m), 7.96-8.06 (2H, m), 8.55 (1H, s), 8.61-8.66 (1H, m).

**[0198]**

#### 35 **Example 10**

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (900 mg), methyl (4-hydroxyphenoxy)acetate (650 mg), triphenylphosphine (930 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.59 g) of diethyl azodicarboxylate in toluene at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 4-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}phenoxy)acetic acid (610 mg, yield 43%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 138-139°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.39 (3H, s), 4.64 (2H, s), 4.94 (2H, s), 6.87-6.97 (4H, m), 7.96-8.06 (2H, m), 8.55 (1H, s), 8.61-8.66 (1H, m).

#### Example 11

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol (740 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (670 mg), triphenylphosphine (700 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.20 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,

1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
5 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-phenyl-3-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)-1H-pyrazol-5-yl]propionic acid (930 mg, yield 72%). The crystals were  
10 recrystallized from ethyl acetate-hexane. melting point: 139-140°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.76-2.06 (4H, m), 2.56-2.70 (2H, m), 2.84-3.02 (4H, m), 4.18-4.32 (2H, m), 5.68 (1H, s), 6.36 (1H, s), 7.28-7.48 (5H, m), 7.66-7.75 (2H, m), 7.85-7.94 (2H, m).

#### 15 **Example 12**

A mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butyl methanesulfonate (700 mg), sodium iodide (300 mg), methyl 4-hydroxybenzoate (290 mg), potassium carbonate (460 mg) and N,N-dimethylformamide (10 ml) was  
20 stirred at 90°C for 5 hours. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column  
25 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (3 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N  
30 Hydrochloric acid (3 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 4-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)benzoic acid (630  
35

mg, yield 81%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 170-171°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.82-2.12 (4H, m), 2.86-2.98 (2H, m), 4.02-4.14 (2H, m), 6.36 (1H, s), 6.88-6.98 (2H, m), 7.66-7.76 (2H, m), 7.85-7.95 (2H, m), 8.00-8.10 (2H, m).

5  
[0199]

### Example 13

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol (700 mg), methyl 4-hydroxyphenylacetate (400 mg), triphenylphosphine (660 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.10 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [4-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)phenyl]acetic acid (810 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 125-126°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.78-2.07 (4H, m), 2.83-2.95 (2H, m), 3.59 (2H, s), 3.94-4.06 (2H, m), 6.36 (1H, s), 6.79-6.91 (2H, m), 7.14-7.26 (2H, m), 7.64-7.76 (2H, m), 7.84-7.96 (2H, m).

### Example 14

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol (700 mg), methyl 3-(4-hydroxyphenyl)propionate (440 mg), triphenylphosphine (650 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution



(1.25 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
5 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture  
10 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)phenyl]propionic  
15 acid (760 mg, yield 72%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 130-131°C.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.80-2.04 (4H, m), 2.56-2.70 (2H, m), 2.82-2.98 (4H, m), 3.94-4.06 (2H, m), 6.36 (1H, s), 6.77-6.88 (2H, m), 7.07-7.17 (2H, m), 7.64-7.76 (2H, m), 7.85-7.96 (2H, m).

#### 20 **Example 15**

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol (700 mg), methyl [2-(4-hydroxyphenoxy)-2-methyl]propionate (500 mg), triphenylphosphine (650 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution  
25 (1.10 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane  
30 (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
35 washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[4-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)phenoxy]propionic acid (860 mg, yield 78%). The crystals were recrystallized

5 from ethyl acetate-hexane. melting point: 103-104°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.53 (6H, s), 1.80-2.06 (4H, m), 2.86-2.98 (2H, m), 3.94-4.04 (2H, m), 6.36 (1H, s), 6.72-6.95 (4H, m), 7.66-7.75 (2H, m), 7.85-7.94 (2H, m).

**[0200]**

#### 10 **Example 16**

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}-1-butanol (700 mg), methyl 3-hydroxyphenylacetate (420 mg), triphenylphosphine (650 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.13 g) of diethyl

15 azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

20 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was

25 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)phenyl]acetic acid (800 mg, yield 78%). The crystals were recrystallized

30 from ethyl acetate-hexane. melting point: 134-135°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.80-2.08 (4H, m), 2.84-2.96 (2H, m), 3.62 (2H, s), 3.96-4.06 (2H, m), 6.36 (1H, s), 6.76-6.91 (3H, m), 7.18-7.30 (1H, m), 7.64-7.76 (2H, m), 7.85-7.96 (2H, m).

#### **Example 17**

35 To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-

isoxazolyl)-1-butanol (700 mg), methyl 2-hydroxyphenylacetate (420 mg), triphenylphosphine (650 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (1.10 g) of diethyl azodicarboxylate in toluene at room temperature and the  
5 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
10 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
15 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl)butoxy)phenyl]acetic acid (800 mg, yield 78%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 122-123°C.  
20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.78-2.06 (4H, m), 2.78-2.92 (2H, m), 3.65 (2H, s), 3.96-4.07 (2H, m), 6.36 (1H, s), 6.80-6.96 (2H, m), 7.14-7.30 (2H, m), 7.64-7.74 (2H, m), 7.84-7.94 (2H, m).

#### Example 18

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-  
25 pyridyl]-1H-pyrazol-4-yl}-1-propanol (330 mg), methyl [2-(4-hydroxyphenoxy)-2-methyl]propionate (250 mg), triphenylphosphine (310 mg) and tetrahydrofuran (7 ml) was dropwise added a 40% solution (550 mg) of diethyl azodicarboxylate in toluene at room temperature and the  
30 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
35 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol

(5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-2-methylpropionic acid (370 mg, yield 71%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 91-92°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.41 (3H, t, J=7.0 Hz), 1.54 (6H, s), 2.00-2.18 (2H, m), 2.54-2.66 (2H, m), 3.98 (2H, t, J=6.2 Hz), 4.35 (2H, q, J=7.0 Hz), 6.76-6.96 (4H, m), 7.81 (1H, d, J=8.8 Hz), 7.91 (1H, dd, J=2.0, 8.8 Hz), 8.18 (1H, s), 8.55 (1H, d, J=2.0 Hz).

【0201】

#### Example 19

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (250 mg), ethyl 3-(2-ethoxy-4-hydroxyphenyl)propionate (250 mg), triphenylphosphine (280 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (480 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(2-ethoxy-4-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-

ylmethoxy)phenyl)propionic acid (310 mg, yield 71%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 151-152°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.42 (3H, t, J=7.0 Hz), 2.39 (3H, s), 2.60-  
5 2.71 (2H, m), 2.84-2.95 (2H, m), 4.01 (2H, q, J=7.0 Hz), 4.94 (2H, s), 6.45-6.54 (2H, m), 7.06-7.14 (1H, m), 7.94-8.08 (2H, m), 8.56 (1H, s), 8.61-8.68 (1H, m).

#### Example 20

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-  
10 isoxazolyl}-1-butanol (1.10 g), methyl 3-(3-hydroxyphenyl)propionate (780 mg), triphenylphosphine (1.10 g) and tetrahydrofuran (15 ml) was dropwise added a 40% solution (1.75 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The  
15 reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (7 ml), tetrahydrofuran  
20 (7 ml) and methanol (7 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (7 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained  
25 colorless crystals were collected by filtration to give 3-[3-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)phenyl]propionic acid (1.26 g, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 131-132°C.

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.80-2.08 (4H, m), 2.60-2.74 (2H, m), 2.85-3.00 (4H, m), 3.96-4.06 (2H, m), 6.36 (1H, s), 6.72-6.84 (3H, m), 7.15-7.27 (1H, m), 7.67-7.76 (2H, m), 7.86-7.95 (2H, m).

#### Example 21

To a mixture of 4-{3-[4-(trifluoromethyl)phenyl]-5-  
35 isoxazolyl}-1-butanol (570 mg), ethyl 3-(2-ethoxy-4-

hydroxyphenyl)propionate (480 mg), triphenylphosphine (550 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (950 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The  
5 reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran  
10 (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
15 collected by filtration to give 3-[2-ethoxy-4-(4-{3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}butoxy)phenyl]propionic acid (260 mg, yield 27%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 105-106°C.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.41 (3H, t, J=7.0 Hz), 1.78-2.08 (4H, m),  
20 2.54-2.72 (2H, m), 2.82-2.97 (4H, m), 3.92-4.08 (4H, m), 6.32-6.44 (3H, m), 6.98-7.10 (1H, m), 7.66-7.76 (2H, m), 7.85-7.95 (2H, m).

**[0202]**

#### **Example 22**

25 To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (410 mg), methyl 3-hydroxyphenylacetate (230 mg), triphenylphosphine (370 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (630 mg) of diethyl azodicarboxylate in toluene at room temperature  
30 and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
35 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol

(5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
5 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (330 mg, yield 56%). The crystals were recrystallized from ethyl acetate-hexane.  
10 melting point: 82-83°C.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47 (6H, d, J=7.0 Hz), 2.02-2.21 (2H, m), 2.69 (2H, t, J=7.4 Hz), 2.94-3.12 (1H, m), 3.64 (2H, s), 4.05 (2H, t, J=6.0 Hz), 6.80-6.92 (3H, m), 7.19-7.30 (1H, m), 7.95 (1H, dd, J=1.8, 8.4 Hz), 8.05 (1H, d, J=8.4 Hz), 8.29 (1H, s),  
15 8.57-8.64 (1H, m).

### Example 23

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (380 mg), methyl 3-(3-hydroxyphenyl)propionate (220 mg), tributylphosphine (260 mg)  
20 and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (350 mg) at room temperature, and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a  
25 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was  
30 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (380 mg, yield 68%). The  
35

crystals were recrystallized from ethyl acetate-hexane.

melting point: 102-103°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.32 (6H, d, J=7.0 Hz), 2.00-2.20 (2H, m),  
2.62-2.76 (4H, m), 2.87-3.13 (3H, m), 4.05 (2H, t, J=6.2 Hz),  
5 6.73-6.86 (3H, m), 7.15-7.26 (1H, m), 7.91-8.08 (2H, m), 8.27  
(1H, s), 8.57-8.63 (1H, m).

#### Example 24

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-  
pyridyl]-1H-pyrazol-4-yl}-1-propanol (520 mg), ethyl 3-(3-  
10 hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (440 mg),  
tributylphosphine (510 mg) and tetrahydrofuran (10 ml) was  
added 1,1'-azodicarbonyldipiperidine (650 mg) at room  
temperature and the mixture was stirred overnight. The  
reaction solution was concentrated. The residue was subjected  
15 to silica gel column chromatography, and a colorless oil was  
obtained from a fraction eluted with ethyl acetate-hexane  
(1:4, volume ratio). A mixture of the obtained oily substance,  
1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran  
(5 ml) and methanol (5 ml) was stirred at room temperature for  
20 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture  
was extracted with ethyl acetate. The ethyl acetate layer was  
washed with saturated aqueous sodium chloride solution, dried  
(MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
collected by filtration to give 3-[3-(3-{3-isopropyl-1-[5-  
25 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)-1-  
phenyl-1H-pyrazol-5-yl]propionic acid (420 mg, yield 48%). The  
crystals were recrystallized from ethyl acetate-hexane.  
melting point: 139-140°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.32 (6H, d, J=7.0 Hz), 2.00-2.20 (2H, m),  
30 2.56-2.76 (4H, m), 2.88-3.12 (3H, m), 4.27 (2H, t, J=6.0 Hz),  
5.72 (1H, s), 7.30-7.50 (5H, m), 7.95 (1H, dd, J=2.6, 9.0 Hz),  
8.04 (1H, d, J=9.0 Hz), 8.27 (1H, s), 8.54-8.61 (1H, m).

【0203】

#### Example 25

35 To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-



pyridyl]-1H-pyrazol-4-yl]-1-propanol (550 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propionate (360 mg), tributylphosphine (530 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room  
5 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,  
10 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
15 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-5-yl]propionic acid (630 mg, yield 77%). The crystals were recrystallized from ethyl acetate-hexane.  
20 melting point: 131-132°C.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.31 (6H, d, J=7.0 Hz), 1.98-2.16 (2H, m), 2.58-3.12 (7H, m), 3.66 (3H, s), 4.16 (2H, t, J=6.2 Hz), 5.49 (1H s), 7.94 (1H, dd, J=1.8, 8.6 Hz), 8.04 (1H, d, J=8.6 Hz), 8.26 (1H, s), 8.56-8.62 (1H, m).

#### 25 **Example 26**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1-methyl-1H-pyrazole-5-carbaldehyde (1.10 g), ethyl diethylphosphonoacetate (690 mg) and N,N-dimethylformamide (15 ml), was added sodium hydride  
30 (60%, in oil, 120 mg) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried  
35 (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica

gel column chromatography, and ethyl (E)-3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1-methyl-1H-pyrazol-5-yl)propenoate (1.03 g, yield 79%) was obtained as colorless crystals from a fraction eluted with  
5 ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 105-106°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.33 (3H, t, J=7.0 Hz), 1.36 (6H, d, J=7.0 Hz), 3.07-3.24 (1H, m), 3.83 (3H, s), 4.27 (2H, q, J=7.0 Hz),  
10 5.14 (2H, s), 5.95 (1H, s), 6.28 (1H, d, J=15.6 Hz), 7.48 (1H, d, J=15.6 Hz), 7.97 (1H, dd, J=2.2, 8.4 Hz), 8.07 (1H, d, J=8.4 Hz), 8.56 (1H, s), 8.60-8.66 (1H, m).

#### Example 27

A mixture of ethyl (E)-3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1-methyl-1H-pyrazol-5-yl)propenoate (900 mg), 5% palladium-carbon (260 mg) and tetrahydrofuran (20 ml) was stirred at room  
15 temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. A mixture of the obtained crystal, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 3 hours.  
20 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1-methyl-1H-pyrazol-5-yl)propionic acid (780 mg, yield 92%).  
25 The crystals were recrystallized from ethyl acetate-hexane. melting point: 141-142°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.36 (6H, d, J=7.0 Hz), 2.62-2.94 (4H, m), 3.06-3.24 (1H, m), 3.69 (3H, s), 5.10 (2H, s), 5.51 (1H, s), 7.98 (1H, dd, J=2.2, 9.2 Hz), 8.07 (1H, d, J=9.2 Hz), 8.53  
35 (1H, s), 8.58-8.67 (1H, m).

【0204】

**Example 28**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (1.20 g), methyl [2-(3-hydroxyphenoxy)-2-methyl]propionate (830 mg), tributylphosphine (1.60 g) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (2.01 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-[3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-2-methylpropionic acid (1.32 g, yield 70%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 101-102°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.32 (6H, d, J=7.0 Hz), 1.63 (6H, s), 2.00-2.18 (2H, m), 2.69 (2H, t, J=7.2 Hz), 2.94-3.12 (1H, m), 4.00 (2H, t, J=6.2 Hz), 6.50-6.70 (3H, m), 7.11-7.24 (1H, m), 7.96 (1H, dd, J=2.2, 8.8 Hz), 8.06 (1H, d, J=8.8 Hz), 8.26 (1H, s), 8.54-8.63 (1H, m).

**Example 29**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (550 mg), methyl [2-(3-hydroxyphenoxy)-2-methyl]propionate (380 mg), tributylphosphine (730 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (910 mg) at room temperature and the mixture was stirred overnight. The

reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-[3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-2-methylpropionic acid (530 mg, yield 62%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 120-121°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.41 (3H, t, J=7.0 Hz), 1.62 (6H, s), 1.96-2.18 (2H, m), 2.62 (2H, t, J=7.0 Hz), 3.97 (2H, t, J=6.2 Hz), 4.35 (2H, q, J=7.0 Hz), 6.48-6.68 (3H, m), 7.08-7.23 (1H, m), 7.84 (1H, d, J=8.8 Hz), 7.93 (1H, dd, J=2.6, 8.8 Hz), 8.16 (1H, s), 8.51-8.56 (1H, m).

### Example 30

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (650 mg), methyl 3-hydroxyphenylacetate (380 mg), tributylphosphine (930 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (1.16 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-

5 yl}propoxy)phenyl]acetic acid (490 mg, yield 53%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 134-135°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.41 (3H, t, J=7.2 Hz), 2.02-2.14 (2H, m), 2.60 (2H, t, J=7.2 Hz), 3.62 (2H, s), 4.01 (2H, t, J=6.3 Hz), 10 4.34 (2H, q, J=7.2 Hz), 6.78-6.88 (3H, m), 7.18-7.28 (1H, m), 7.80 (1H, d, J=8.7 Hz), 7.90 (1H, dd, J=2.4, 8.7 Hz), 8.17 (1H, s), 8.52-8.57 (1H, m).

**[0205]**

### **Example 31**

15 To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (620 mg), methyl 2-hydroxyphenylacetate (340 mg), tributylphosphine (800 mg) and tetrahydrofuran (10 ml) was added 1,1'-  
azodicarbonyldipiperidine (1.00 g) at room temperature and the  
20 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
25 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
30 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (310 mg, yield 35%). The crystals were recrystallized from ethyl acetate-hexane.  
35 melting point: 83-84°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.40 (3H, t, J=7.0 Hz), 2.00-2.18 (2H, m), 2.61 (2H, t, J=7.0 Hz), 3.68 (2H, s), 4.02 (2H, t, J=6.2 Hz), 4.34 (2H, q, J=7.0 Hz), 6.80-6.96 (2H, m), 7.14-7.28 (2H, m), 7.80 (1H, d, J=8.8 Hz), 7.90 (1H, dd, J=2.2, 8.8 Hz), 8.20  
5 (1H, s), 8.49-8.56 (1H, m).

### Example 32

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (500 mg), methyl [2-(3-hydroxyphenoxy)-2-methyl]propionate (430 mg),  
10 triphenylphosphine (570 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (980 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column  
15 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N  
20 Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}phenoxy)propionic acid (600 mg, yield 71%). The  
25 crystals were recrystallized from ethyl acetate-hexane. melting point: 152-153°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.64 (6H, s), 2.38 (3H, s), 4.99 (2H, s),  
30 6.52-6.68 (3H, m), 7.15 (1H, t, J=8.1 Hz), 7.98-8.08 (2H, m), 8.58-8.68 (2H, m).

### Example 33

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (550 mg), methyl 3-(3-hydroxyphenyl)propionate (330 mg), tributylphosphine (700 mg)  
35

and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (880 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propionic acid (590 mg, yield 73%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 88-89°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.41 (3H, t, J=7.0 Hz), 2.00-2.18 (2H, m), 2.54-2.76 (4H, m), 2.88-3.02 (2H, m), 4.00 (2H, t, J=6.2 Hz), 4.35 (2H, q, J=7.0 Hz), 6.71-6.88 (3H, m), 7.14-7.24 (1H, m), 7.77-7.96 (2H, m), 8.17 (1H, s), 8.52-8.60 (1H, m).

【0206】

#### Example 34

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (520 mg), methyl [2-(4-hydroxyphenoxy)-2-methyl]propionate (430 mg), triphenylphosphine (580 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (980 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium

hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
5 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-(4-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}phenoxy)propionic acid (330 mg, yield 38%). The  
10 crystals were recrystallized from isopropyl ether-hexane. melting point: 106-107°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.55 (6H, s), 2.39 (3H, s), 4.94 (2H, s), 6.85-6.99 (4H, m), 7.95-8.07 (2H, m), 8.55 (1H, s), 8.61-8.66 (1H, m).

15 **Example 35**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(2-ethoxy-4-hydroxyphenyl)propionate (460 mg), tributylphosphine (650 mg) and tetrahydrofuran (10 ml) was added 1,1'-  
20 azodicarbonyldipiperidine (820 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
25 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
30 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-ethoxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (540 mg, yield 67%). The  
35 crystals were recrystallized from ethyl acetate-hexane.



melting point: 96-97°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.37-1.48 (6H, m), 2.02-2.16 (2H, m), 2.56-2.69 (4H, m), 2.83-2.94 (2H, m), 3.93-4.06 (4H, m), 4.34 (2H, q, J=7.2 Hz), 6.34-6.47 (2H, m), 7.02 (1H, d, J=8.4 Hz), 7.76-7.94 (2H, m), 8.17 (1H, s), 8.50-8.58 (1H, m).

#### Example 36

To a mixture of 1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazole-5-carbaldehyde (2.00 g), ethyl diethylphosphonoacetate (1.35 g) and N,N-dimethylformamide (30 ml) was added sodium hydride (60%, in oil, 240 mg) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and ethyl (E)-3-(1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazol-5-yl)propenoate (2.14 g, yield 80%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 173-174°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.33 (3H, t, J=7.2 Hz), 2.40 (3H, s), 3.83 (3H, s), 4.26 (2H, q, J=7.2 Hz), 5.11 (2H, s), 5.94 (1H, s), 6.27 (1H, d, J=15.9 Hz), 7.47 (1H, d, J=15.9 Hz), 7.94-8.04 (2H, m), 8.57 (1H, s), 8.60-8.65 (1H, m).

【0207】

#### Example 37

A mixture of ethyl (E)-3-(1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazol-5-yl)propenoate (600 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at 60°C for 2 hours. 1N Hydrochloric acid (10 ml) was added and the mixture was extracted with ethyl acetate.

The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (E)-3-(1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazol-5-yl)propenoic acid (520 mg, yield 93%). The crystals were recrystallized from acetone-hexane. melting point: 208-209°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.41 (3H, s), 3.85 (3H, s), 5.13 (2H, s), 6.00 (1H, s), 6.28 (1H, d, J=15.8 Hz), 7.57 (1H, d, J=15.8 Hz), 7.93-8.07 (2H, m), 8.58 (1H, s), 8.60-8.66 (1H, m).

### Example 38

A mixture of ethyl (E)-3-(1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazol-5-yl)propenoate (1.25 g), 5% palladium-carbon (600 mg) and tetrahydrofuran (30 ml) was stirred at room temperature for 1 hour under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazol-5-yl)propionic acid (1.13 g, yield 96%). The crystals were recrystallized from acetone-hexane. melting point: 154-155°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.39 (3H, s), 2.64-2.77 (2H, m), 2.81-2.94 (2H, m), 3.68 (3H, s), 5.07 (2H, s), 5.51 (1H, s), 7.94-8.07 (2H, m), 8.54 (1H, s), 8.60-8.65 (1H, m).

### Example 39

To a mixture of {3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (1.50 g), methyl 3-hydroxy-

1-methyl-1H-pyrazole-5-carboxylate (830 mg), triphenylphosphine (1.40 g) and tetrahydrofuran (30 ml) was dropwise added a 40% solution (2.35 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1-methyl-1H-pyrazole-5-carboxylate (2.00 g, yield 90%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 114-115°C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.36 (6H, d, J=6.9 Hz), 3.10-3.24 (1H, m), 3.87 (3H, s), 4.06 (3H, s), 5.15 (2H, s), 6.21 (1H, s), 7.94-8.10 (2H, m), 8.57 (1H, s), 8.61-8.66 (1H, m).

**[0208]**

#### **Example 40**

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (3.95 g), methyl 3-hydroxy-1-methyl-1H-pyrazole-5-carboxylate (2.39 g), triphenylphosphine (4.50 g) and tetrahydrofuran (50 ml) was dropwise added a 40% solution (7.60 g) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and methyl 1-methyl-3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-ylmethoxy}-1H-pyrazole-5-carboxylate (4.90 g, yield 81%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 130-131°C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.40 (3H, s), 3.86 (3H, s), 4.05 (3H, s), 5.12 (2H, s), 6.20 (1H, s), 7.94-8.06 (2H, m), 8.57 (1H, s), 8.59-8.67 (1H, m).

#### **Example 41**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (0.40 g), methyl [2-(3-hydroxyphenoxy)-2-methyl]propionate (280 mg), tributylphosphine (500 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl]propoxy)phenoxy]propionic acid (300 mg, yield 48%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 99-100°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (3H, t, J=7.0 Hz), 1.61 (6H, s), 1.60-1.83 (2H m), 1.98-2.10 (2H, m), 2.55-2.76 (4H, m), 3.98 (2H, t, J=6.2 Hz), 6.50-6.70 (3H, m), 7.11-7.24 (1H, m), 7.90-8.08 (2H, m), 8.27 (1H, s), 8.55-8.64 (1H, m).

#### Example 42

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (440 mg), tributylphosphine (650 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane

(1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture  
5 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1-  
10 phenyl-1H-pyrazol-5-yl]propionic acid (460 mg, yield 55%). The crystals were recrystallized from ethyl acetate-hexane.  
melting point: 121-122°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.42 (3H, t, J=7.0 Hz), 1.96-2.18 (2H, m), 2.52-2.71 (4H, m), 2.88-3.00 (2H, m), 4.17-4.28 (2H, m), 4.35  
15 (2H, q, J=7.0 Hz), 5.71 (1H, s), 7.27-7.50 (5H, m), 7.76-7.95 (2H, m), 8.17 (1H, s), 8.50-8.56 (1H, m).

【0209】

#### Example 43

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (540 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (450 mg), tributylphosphine (700 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (860 mg) at room temperature and the mixture was stirred overnight. The  
20 reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran  
30 (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
35 collected by filtration to give 3-[1-phenyl-3-(3-{3-propyl-1-

[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propionic acid (630 mg, yield 69%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 149-150°C.

5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.00 (3H, t, J=7.2 Hz), 1.62-1.85 (2H, m), 1.98-2.18 (2H, m), 2.55-2.71 (6H, m), 2.88-3.02 (2H, m), 4.18-4.30 (2H, m), 5.71 (1H, s), 7.27-7.51 (5H, m), 7.89-8.06 (2H, m), 8.29 (1H, s), 8.55-8.62 (1H, m).

#### Example 44

10 To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (550 mg), methyl 3-hydroxyphenylacetate (300 mg), tributylphosphine (740 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (890 mg) at room temperature and the  
15 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
20 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
25 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (630 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane.  
30 melting point: 106-107°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.00 (3H, t, J=7.0 Hz), 1.62-1.82 (2H, m), 2.00-2.18 (2H, m), 2.55-2.74 (4H, m), 3.62 (2H, s), 4.03 (2H, t, J=6.2 Hz), 6.70-6.92 (3H, m), 7.17-7.32 (1H, m), 7.90-8.05 (2H, m), 8.30 (1H, s), 8.58-8.64 (1H, m).

#### 35 Example 45

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propionate (320 mg), tributylphosphine (650 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (800 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-methyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propionic acid (550 mg, yield 74%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 80-81°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (3H, t, J=7.4 Hz), 1.60-1.84 (2H, m), 1.95-2.14 (2H, m), 2.54-2.93 (8H, m), 3.66 (3H, s), 4.08-4.20 (2H, m), 5.48 (1H, s), 7.90-8.06 (2H, m), 8.28 (1H, s), 8.57-8.64 (1H, m).

【0210】

#### Example 46

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (550 mg), methyl 4-hydroxyphenylacetate (300 mg), tributylphosphine (750 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (890 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a

fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N  
5 Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [4-(3-{3-propyl-1-[5-  
10 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (590 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 101-102°C.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (3H, t, J=7.4 Hz), 1.62-1.84 (2H m),  
15 2.01-2.19 (2H, m), 2.55-2.73 (4H, m), 3.60 (2H, s), 3.96-4.06 (2H, m), 6.82-6.92 (2H, m), 7.14-7.24 (2H, m), 7.90-8.06 (2H, m), 8.30 (1H, s), 8.57-8.64 (1H, m).

#### Example 47

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-  
20 pyridyl]-1H-pyrazol-4-yl}-1-propanol (550 mg), methyl 2-hydroxyphenylacetate (300 mg), tributylphosphine (750 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
azodicarbonyldipiperidine (900 mg) at room temperature and the mixture was stirred overnight. The reaction solution was  
25 concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol  
30 (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
35 collected by filtration to give [2-(3-{3-propyl-1-[5-



(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (620 mg, yield 79%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 100-101°C.

5 **Example 48**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propanoate (346 mg), tributylphosphine (790  $\mu$ L) and tetrahydrofuran (53 ml) was  
10 added 1,1'-azodicarbonyldipiperidine (800 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
15 obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (25 ml) was added and the  
20 mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-5-yl]propanoic acid (370 mg, yield 50%). melting point: 137-  
25 138°C.

[0211]

**Example 49**

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (437 mg), tributylphosphine (761  $\mu$ L) and tetrahydrofuran (50 ml) was  
30 added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The  
35 reaction solution was concentrated. The residue was subjected

to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 2 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[3-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1-phenyl-1H-pyrazol-5-yl]propanoic acid (594 mg, yield 72%). melting point: 137-138°C.

#### Example 50

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propanoate (333 mg), tributylphosphine (761 µL) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 2 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[3-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1-methyl-1H-pyrazol-5-yl]propanoic acid (366 mg, yield 50%). melting point: 113-

114°C.

#### Example 51

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 3-hydroxyphenylacetate (279 mg), tributylphosphine (761  $\mu$ L) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:20, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) at room temperature for 6 hours was stirred. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were recrystallized from diisopropyl ether-hexane, [3-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)butoxy)phenyl]acetic acid (165 mg, yield 23%). melting point: 114-115°C.

【0212】

#### Example 52

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 2-hydroxyphenylacetate (279 mg), tributylphosphine (761  $\mu$ L) and tetrahydrofuran (80 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (50 ml) and

ethanol (25 ml) was stirred at room temperature for 2 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
5 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [2-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (376 mg, yield 53%). melting point: 125-126°C.

#### 10 **Example 53**

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 4-hydroxyphenylacetate (279 mg), tributylphosphine (761 µL) and tetrahydrofuran (76 ml) was added 1,1'-  
15 azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).  
20 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (50 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (50 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
25 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [4-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (335 mg, yield 47%). melting  
30 point: 130-131°C.

#### **Example 54**

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 2-(3-hydroxyphenoxy)-2-methylpropanoate (353 mg), tributylphosphine  
35 (761 µL) and tetrahydrofuran (76 ml) was added 1,1'-

azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a  
5 fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (50 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (50 ml) was added and the mixture was  
10 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane  
15 (1:1, volume ratio). The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 2-[3-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenoxy]-2-methylpropanoic acid (258 mg, yield 33%). melting point: 81-82°C.

20    **[0213]**

**Example 55**

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 3-(4-hydroxyphenyl)propanoate (303 mg), tributylphosphine (761  $\mu$ L)  
25 and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a  
30 fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (50 ml), tetrahydrofuran (50 ml) and ethanol (25 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (50 ml) was added and the mixture was  
35 extracted with ethyl acetate. The ethyl acetate layer was

washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[4-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]propanoic acid (231 mg, yield 32%). melting point: 144-145°C.

#### Example 56

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (300 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (285 mg), tributylphosphine (496 µL) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (503 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (15 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[3-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)-1-phenyl-1H-pyrazol-5-yl]propanoic acid (372 mg, yield 72%). melting point: 155-156°C.

#### Example 57

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (300 mg), methyl 2-hydroxyphenylacetate (183 mg), tributylphosphine (496 µL) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (502 mg) at room temperature and the mixture was stirred overnight. The reaction solution was

concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
5 hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
10 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [2-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)phenyl]acetic acid (242 mg, yield 56%). melting point: 134-135°C.

15    **[0214]**

**Example 58**

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (437 mg),  
20 tributylphosphine (761 µL) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
25 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the  
30 mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[1-phenyl-3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1H-

pyrazol-5-yl]propanoic acid (505 mg, yield 61%). melting point: 123-124°C.

#### Example 59

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 3-hydroxyphenylacetate (508 mg), tributylphosphine (761  $\mu$ L) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3.5 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (330 mg, yield 47%). melting point: 96-97°C.

#### Example 60

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 2-hydroxyphenylacetate (279 mg), tributylphosphine (761  $\mu$ L) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and



extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [4-methoxy-3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (388 mg, yield 52%). melting point: 147-148°C.

【0216】

#### Example 64

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), ethyl 3-(4-hydroxy-2-methylphenyl)propanoate (350 mg), tributylphosphine (761  $\mu$ L) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[2-methyl-4-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]propanoic acid (323 mg, yield 43%). melting point: 105-107°C.

#### Example 65

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (480 mg), ethyl 3-(4-hydroxy-2-methylphenyl)propanoate (351 mg), tributylphosphine (763  $\mu$ L) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (773 mg) at room temperature and the

mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio).  
5 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
10 washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[2-methyl-4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (147 mg, yield 20%).  
15 melting point: 124-126°C.

#### Example 66

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl (3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acetate (390 mg),  
20 tributylphosphine (761  $\mu\text{L}$ ) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
25 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the  
30 mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [1-phenyl-3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1H-  
35 (trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1H-

pyrazol-4-yl]acetic acid (600 mg, yield 74%). melting point: 114-115°C.

【0217】

**Example 67**

5 To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (480 mg), methyl (3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acetate (391 mg), tributylphosphine (763  $\mu$ L) and tetrahydrofuran (77 ml) was added 1,1'-azodicarbonyldipiperidine (773 mg) at room  
10 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,  
15 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride  
20 solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [1-phenyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (601 mg, yield 76%). melting point:  
25 123-124°C.

**Example 68**

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl (3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acetate (390 mg),  
30 tributylphosphine (761  $\mu$ L) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
35 obtained from a fraction eluted with ethyl acetate-hexane

(1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the  
5 mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [3-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-  
10 pyridinyl]-1H-pyrazol-4-yl}butoxy)-1-phenyl-1H-pyrazol-4-yl]acetic acid (471 mg, yield 58%). melting point: 119-120°C.

#### Example 69

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (350 mg), methyl 3-(4-  
15 hydroxy-2-methoxyphenyl)propanoate (674 mg), tributylphosphine (799  $\mu$ L) and tetrahydrofuran (53 ml) was added 1,1'-azodicarbonyldipiperidine (809 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column  
20 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours.  
25 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[4-(4-{3-  
30 isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-2-methoxyphenyl]propanoic acid (319 mg, yield 59%). melting point: 125-126°C.

【0218】

#### Example 70

35 To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-

pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propanoate (333 mg), tributylphosphine (761  $\mu$ L) and tetrahydrofuran (76 ml) was added 1,1'-azodicarbonyldipiperidine (771 mg) at room  
5 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance,  
10 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride  
15 solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[1-methyl-3-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1H-pyrazol-5-yl]propanoic acid (345 mg, yield 47%). melting  
20 point: 122-123°C.

#### Example 71

To a mixture of 3-{3-(benzyloxy)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (247 mg),  
25 tributylphosphine (394  $\mu$ L) and tetrahydrofuran (40 ml) was added 1,1'-azodicarbonyldipiperidine (399 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
30 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the  
35 mixture was extracted with ethyl acetate. The ethyl acetate

layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[3-(3-{3-(benzyloxy)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1-phenyl-1H-pyrazol-5-yl]propanoic acid (378 mg, yield 81%). melting point: 159-161°C.

#### Example 72

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (400 mg), methyl (3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acetate (339 mg), tributylphosphine (662 µL) and tetrahydrofuran (66 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [3-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)-1-phenyl-1H-pyrazol-4-yl]acetic acid (544 mg, yield 82%). melting point: 135-137°C.

【0219】

#### Example 73

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (400 mg), methyl 4-hydroxyphenylacetate (243 mg), tributylphosphine (662 µL) and tetrahydrofuran (66 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature and the

mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A  
5 mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
10 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [4-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)phenyl]acetic acid (123 mg, yield 21%). melting  
15 point: 142-143°C.

#### **Example 74**

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (400 mg), methyl 2-(3-hydroxyphenoxy)-2-methylpropanoate (335 mg), tributylphosphine  
20 (662 µL) and tetrahydrofuran (66 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a  
25 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was  
30 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane  
35 (1:1, volume ratio). The obtained colorless crystals were

recrystallized from ethyl acetate-hexane to give 2-[3-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)phenoxy]-2-methylpropanoic acid (169 mg, yield 26%). melting point: 89-90°C.

5 **Example 75**

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (350 mg), methyl 3-(4-hydroxy-2-methoxyphenyl)propanoate (733 mg), tributylphosphine (868  $\mu$ L) and tetrahydrofuran (58 ml) was added 1,1'-  
10 azodicarbonyldipiperidine (879 mg) at room temperature overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale-yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A  
15 mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 days. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
20 washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:1.5, volume ratio). The obtained colorless crystals were  
25 recrystallized from ethyl acetate-hexane to give 3-[4-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)-2-methoxyphenyl]propanoic acid (337 mg, yield 61%). melting point: 147-148°C.

**[0220]**

30 **Example 76**

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanol (400 mg), ethyl 3-(4-hydroxy-2-methylphenyl)propaneacetate (332 mg), tributylphosphine (662  $\mu$ L) and tetrahydrofuran (66 ml) was  
35 added 1,1'-azodicarbonyldipiperidine (670 mg) at room



temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[4-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)-2-methylphenyl]propanoic acid (210 mg, yield 34%). melting point: 117-119°C.

#### **Example 77**

A mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyl methanesulfonate (500 mg), sodium hydride (60%, in oil, 74.0 mg), N,N-dimethylformamide (10 ml) was stirred at room temperature for 30 minutes and a solution of ethyl 3-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]propanoate (350 mg) in N,N-dimethylformamide (2 ml) was added. After stirring overnight, water was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The

obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[3-(4-fluorophenyl)-1-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyl)-1H-pyrazol-4-yl]propanoic acid (395 mg, yield 59%). melting point: 119-121°C.

#### Example 78

A mixture of ethyl 3-(3-ethoxy-1H-pyrazol-4-yl)propanoate (500 mg), sodium hydride (60%, in oil, 113 mg) and N,N-dimethylformamide (22 ml) was stirred at room temperature for 1 hour and 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyl methanesulfonate (870 mg) was added. After stirring the resulting mixture overnight, 0.1N aqueous hydrochloric acid solution (100 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 3 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.39 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature for 1 hour and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give sodium 3-[3-ethoxy-1-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyl)-1H-pyrazol-4-yl]propanoate (657 mg, yield 59%). melting point: 250-251°C.

[0221]

#### Example 79

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (470 mg), ethyl 4-hydroxy-3-methoxyphenylacetate (320 mg), tributylphosphine (610 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
5 azodicarbonyldipiperidine (760 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
10 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
15 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (550 mg, yield 77%). The  
20 crystals were recrystallized from ethyl acetate-hexane. melting point: 121-122°C.

#### **Example 80**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (510 mg), methyl 3-  
25 hydroxy-4-methoxyphenylacetate (799 mg), tributylphosphine (1.01 ml) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (1.03 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column  
30 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N  
35 Hydrochloric acid (30 ml) was added and the mixture was

extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [4-methoxy-3-  
5 (3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (451 mg, yield 58%). melting point: 124-126°C.

#### **Example 81**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-  
10 pyridinyl]-1H-pyrazol-4-yl}-1-propanol (560 mg), ethyl 3-(5-hydroxy-2-methoxyphenyl)propanoate (441 mg), tributylphosphine (892 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (903 mg) at room temperature and the mixture was stirred overnight. The reaction solution was  
15 concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) A mixture  
20 of was stirred at room temperature for 5 hours. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica  
25 gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-[2-methoxy-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-  
30 4-yl}propoxy)phenyl]propanoic acid (407 mg, yield 46%). melting point: 104-106°C.

【0222】

#### **Example 82**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-  
35 pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-(4-

hydroxyphenyl)propionate (300 mg), tributylphosphine (700 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was  
5 concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol  
10 (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
15 collected by filtration to give 3-[4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (650 mg, yield 88%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 118-119°C.

20 **Example 83**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-(2-hydroxyphenyl)propionate (300 mg), tributylphosphine (700 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
25 azodicarbonyldipiperidine (800 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
30 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
35 washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (420 mg, yield 57%). The  
5 crystals were recrystallized from ethyl acetate-hexane. melting point: 87-88°C.

#### **Example 84**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-(3-  
10 hydroxyphenyl)propionate (300 mg), tributylphosphine (700 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (800 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column  
15 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N  
20 Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-  
25 yl}propoxy)phenyl]propionic acid (520 mg, yield 71%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 97-98°C.

**[0223]**

#### **Example 85**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-(4-  
hydroxy-2-methoxyphenyl)propionate (340 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
35 azodicarbonyldipiperidine (810 mg) at room temperature and the

mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
5 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
10 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-methoxyphenyl]propionic acid (530 mg, yield 67%). The crystals  
15 were recrystallized from ethyl acetate-hexane. melting point: 120-121°C.

#### **Example 86**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (510 mg), methyl 3-(4-  
20 hydroxy-2-methoxyphenyl)propionate (360 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column  
25 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N  
30 Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-methoxy-4-(3-{3-propyl-1-  
35 [5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-

yl)propoxy)phenyl]propionic acid (520 mg, yield 65%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 114-115°C.

#### Example 87

5 To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (510 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (290 mg), tributylphosphine (680 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (860 mg) at room  
10 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,  
15 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
20 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [1-methyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (570 mg, yield 77%). The crystals were recrystallized from ethyl acetate-hexane. melting point:  
25 119-120°C.

【0224】

#### Example 88

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl 4-  
30 hydroxyphenylacetate (270 mg), tributylphosphine (620 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (780 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column  
35 chromatography, and a colorless oil was obtained from a



fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N  
5 Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [4-(4-{3-propyl-1-[5-  
10 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (410 mg, yield 58%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 121-122°C.

#### Example 89

15 To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-butanol (510 mg), methyl 3-(4-hydroxy-2-methoxyphenyl)propionate (330 mg), tributylphosphine (630 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (790 mg) at room temperature and the  
20 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
25 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
30 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-methoxy-4-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}butoxy)phenyl]propionic acid (510 mg, yield 65%). The  
35 crystals were recrystallized from ethyl acetate-hexane. melting point: 91-92°C.

### Example 90

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (190 mg), methyl 2-fluoro-5-hydroxyphenylacetate (110 mg), tributylphosphine (250 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (310 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-fluoro-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (220 mg, yield 79%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 111-112°C.

【0225】

### Example 91

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (390 mg), methyl 4-fluoro-3-hydroxyphenylacetate (230 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol

(5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
5 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [4-fluoro-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (220 mg, yield 79%). The crystals were recrystallized from ethyl acetate-hexane.  
10 melting point: 88-89°C.

#### Example 92

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(3-hydroxy-5-methoxyphenyl)propionate (380 mg), tributylphosphine  
15 (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a  
20 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and ethanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was  
25 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-methoxy-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-  
30 yl}propoxy)phenyl]propionic acid (380 mg, yield 48%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 98-99°C.

#### Example 93

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(3-

hydroxy-4-methoxyphenyl)propionate (360 mg), tributylphosphine (650 mg) and tetrahydrofuran (35 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-methoxy-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (280 mg, yield 70%). melting point: 147-148°C.

【0226】

**Example 94**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (650 mg), methyl 4-hydroxy-2-methylphenylacetate (390 mg), tributylphosphine (840 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (1050 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-methyl-4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (590 mg, yield 62%). The  
5 crystals were recrystallized from ethyl acetate-hexane. melting point: 134-135°C.

#### Example 95

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (470 mg), methyl 4-  
10 hydroxy-2-methoxyphenylacetate (300 mg), tributylphosphine (610 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (760 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column  
15 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N  
20 Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-methoxy-4-(3-{3-propyl-1-  
25 [5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (580 mg, yield 81%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 135-136°C.

#### Example 96

30 To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (470 mg), ethyl 3-(4-hydroxy-3-methoxyphenyl)propionate (350 mg), tributylphosphine (610 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (760 mg) at room temperature and the  
35 mixture was stirred overnight. The reaction solution was

concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
5 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and  
10 concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-methoxy-4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (590 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane.  
15 melting point: 126-127°C.

【0227】

#### Example 97

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (580 mg), methyl (5-  
20 hydroxy-2-methoxyphenyl)acetate (400 mg), tributylphosphine (924  $\mu$ L) and tetrahydrofuran (90 ml) was added 1,1'-azodicarbonyldipiperidine (936 mg) at room temperature and the mixture was stirred for 3 days. The reaction solution was concentrated. The residue was subjected to silica gel column  
25 chromatography, and a pale-yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred at room temperature overnight. 1N  
30 Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained pale-yellow crystals were recrystallized from ethyl acetate-hexane to give [2-  
35 methoxy-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-

pyrazol-4-yl}propoxy)phenyl]acetic acid (483 mg, yield 55%) as colorless crystals. melting point: 135-136°C.

**Example 98**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-(4-hydroxy-2-ethoxyphenyl)propanoate (395 mg), tributylphosphine (797  $\mu$ L) and tetrahydrofuran (80 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-ethoxy-4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (442 mg, yield 55%) as colorless crystals. melting point: 119-120°C.

**Example 99**

To a mixture of 3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 3-(4-hydroxy-2-ethoxyphenyl)propanoate (260 mg), tributylphosphine (480  $\mu$ L) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (30 ml), tetrahydrofuran (30 ml) and ethanol (30 ml)

was stirred overnight at room temperature. 1N Hydrochloric acid (30 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-ethoxy-4-(3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (373 mg, yield 60%) as colorless crystals. melting point: 135-136°C.

10    **[0228]**

**Example 100**

A mixture of ethyl 2-{3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy}-2-methylpropanoate (300 mg), sodium hydride (60%, in oil, 63.6 mg), N,N-dimethylformamide (10 ml) was stirred at room temperature for 30 minutes and iodocyclopentane (184 µL) was added. After stirring overnight, saturated aqueous ammonia chloride was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the obtained residue, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (645 µL), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour and concentrated. To a mixture of the obtained residue and water (25 ml) was added calcium chloride (69.0 mg) dissolved in a small amount of water, and the mixture was stirred overnight at room temperature. The



resulting white precipitates were collected by filtration to give calcium 2-{3-[3-(1-cyclopentyl-3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy}-2-methylpropanoate (256 mg, yield 74%) as amorphous.

5 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.25 (3H, t, J = 6.9 Hz), 1.41 (6H, s), 1.52 - 1.61 (2H, m), 1.67 - 2.00 (8H, m), 2.32 - 2.39 (2H, m), 3.83 - 3.90 (2H, m), 4.09 (2H, q, J = 6.9 Hz), 4.34 - 4.45 (1H, m), 6.34 - 6.44 (3H, m), 6.96 - 7.04 (1H, m), 7.35 (1H, s).

#### 10 **Example 101**

To a mixture of 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (420 mg), ethyl 2-(3-hydroxyphenoxy)-2-methylpropanoate (419 mg), tributylphosphine (847 μL) and tetrahydrofuran (34 ml) was added 1,1'-

15 azodicarbonyldipiperidine (858 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio).

20 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
25 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 2-(3-{3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy}phenoxy)-2-methylpropanoic acid (291 mg, yield 40%). melting point: 99-  
30 101°C.

#### **Example 102**

A mixture of ethyl 2-{3-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]phenoxy}-2-methylpropanoate (740 mg), sodium hydride (60%, in oil, 90.8 mg), N,N-dimethylformamide (20 ml) was  
35 stirred at room temperature for 30 minutes and 2-chloro-5-

(trifluoromethyl)pyridine (412 mg) was added. After stirring the reaction mixture overnight, saturated aqueous ammonia chloride was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 2.5 days. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (893  $\mu$ L), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour and concentrated. To a mixture of the obtained residue and water (25 ml) was added calcium chloride (90.8 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The resulting white precipitates were collected by filtration to give calcium 2-[3-(4-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenoxy]-2-methylpropanoate (394 mg, yield 39%) as amorphous.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$ : 1.36 (3H, t, J = 7.2 Hz), 1.40 (6H, s), 1.62 - 1.78 (4H, m), 2.36 - 2.46 (2H, m), 3.85 - 3.94 (2H, m), 4.31 (2H, q, J = 7.2 Hz), 6.34 - 6.44 (3H, m), 6.95 - 7.04 (1H, m), 7.79 (1H, d, J = 8.7 Hz), 8.20 - 8.27 (1H, m), 8.32 (1H, s), 8.69 - 8.74 (1H, m).

【0229】

**Example 103**

To a mixture of 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (300 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (346 mg), tributylphosphine (603  $\mu$ L) and tetrahydrofuran (25 ml) was added 1,1'-  
5 azodicarbonyldipiperidine (611 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume  
10 ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
15 washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-(3-{3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy}-1-phenyl-1H-pyrazol-5-yl)propanoic acid (483 mg, yield 87%). melting  
20 point: 156-157°C.

#### **Example 104**

A mixture of ethyl 3-{3-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]-1-phenyl-1H-pyrazol-5-yl}propanoate (900 mg), sodium hydride (60%, in oil, 101 mg), N,N-dimethylformamide  
25 (20 ml) was stirred at room temperature for 30 minutes. 2-Chloro-5-(trifluoromethyl)pyridine (459 mg) was added. After stirring the obtained mixture overnight, saturated aqueous ammonia chloride was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with  
30 saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. A mixture of the obtained yellow oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the  
35 mixture was extracted with ethyl acetate. The ethyl acetate

layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give 3-[3-(4-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)-1-phenyl-1H-pyrazol-5-yl]propanoic acid (640 mg, yield 56%) as colorless crystals. melting point: 138-139°C.

#### 10 **Example 105**

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (512 mg), ethyl 2-(3-hydroxyphenoxy)-2-methylpropanoate (401 mg), tributylphosphine (812  $\mu$ L) and tetrahydrofuran (35 ml) was added 1,1'-azodicarbonyldipiperidine (823 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (995  $\mu$ L), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium chloride (110 mg) dissolved in water (5 ml) and the mixture was stirred overnight at room temperature. The resulting white

precipitates were collected by filtration to give calcium 2-[3-(3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-2-methylpropanoate (440 mg, yield 53%) as amorphous.

5 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.28 - 1.48 (3H, m), 1.41 (6H, s), 1.87 - 2.08 (2H, m), 2.41 - 2.56 (2H, m), 3.86 - 4.00 (2H, m), 4.20 - 4.39 (2H, m), 6.31 - 6.52 (3H, m), 6.93 - 7.10 (1H, m), 7.69 - 7.96 (4H, m), 8.38 (1H, s).

【0230】

#### 10 **Example 106**

To a mixture of 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (300 mg), methyl 3-hydroxyphenylacetate (402 mg), tributylphosphine (603 μL) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (611 mg) at room  
15 temperature and the mixture was stirred for 3 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance,  
20 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride  
25 solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless oil was recrystallized from diisopropyl ether-hexane to give (3-{3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetic acid (247 mg, yield 53%) as colorless crystals. melting point: 66-67°C.

#### 30 **Example 107**

A mixture of methyl 3-{2-ethoxy-4-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]phenyl}propanoate (860 mg), sodium hydride (60%, in oil, 106 mg), N,N-dimethylformamide (25 ml) was stirred at room temperature for 30 minutes and 2-chloro-5-  
35 (trifluoromethyl)pyridine (479 mg) was added. After stirring

overnight, saturated aqueous ammonia chloride was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. A mixture  
5 of the obtained yellow oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was  
10 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume  
15 ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give 3-[2-ethoxy-4-(4-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]propanoic acid (718 mg, yield 63%) as colorless crystals. melting point: 101-102°C.

#### **Example 108**

20 To a mixture of 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (300 mg), methyl 3-(2-ethoxy-4-hydroxyphenyl)propanoate (298 mg), tributylphosphine (603  $\mu\text{L}$ ) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (611 mg) at room temperature and the  
25 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
30 hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
35 ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were

recrystallized from ethyl acetate-hexane to give 3-(2-ethoxy-4-{3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy}phenyl)propanoic acid (323 mg, yield 61%). melting point: 110-111°C.

5     **[0231]**

**Example 109**

To a mixture of 3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (300 mg), ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (298 mg), tributylphosphine (603  $\mu$ L) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (611 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give 3-(4-{3-[3-ethoxy-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)propanoic acid (416 mg, yield 81%). melting point: 92-93°C.

**Example 110**

A mixture of ethyl 3-{3-ethoxy-1-[4-(3-ethoxy-1H-pyrazol-4-yl)butyl]-1H-pyrazol-4-yl}propanoate (680 mg), sodium hydride (60%, in oil, 86.4 mg), N,N-dimethylformamide (20 ml) was stirred at room temperature for 30 minutes and 2-chloro-5-(trifluoromethyl)pyridine (391 mg) was added. After stirring the obtained mixture for 7 hours, saturated aqueous ammonia chloride was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated

aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. A mixture of the obtained yellow oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature  
5 for 5 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless  
10 oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and concentrated. To a mixture of  
15 the obtained residue and water (50 ml) was added calcium chloride (134 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The resulting white precipitates were collected by filtration to give calcium 3-[3-ethoxy-1-(4-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butyl)-1H-pyrazol-4-yl]propanoate (654 mg, yield 71%) as amorphous.  
20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.22 (3H, t, J = 6.9 Hz), 1.36 (3H, t, J = 6.9 Hz), 1.40 - 1.54 (2H, m), 1.66 - 1.78 (2H, m), 2.26 - 2.44 (4H, m), 2.46 - 2.58 (2H, m), 3.69 - 3.78 (2H, m), 4.11 (2H, q, J = 6.9 Hz), 4.27 (2H, q, J = 6.9 Hz), 6.93 (1H, s), 7.71 (1H, d, J = 8.4 Hz), 7.79 - 7.85 (1H, m), 8.05 (1H, s), 8.44 - 8.49 (1H, m).

#### Example 111

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (157 mg),  
30 ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propanoate (130 mg), tributylphosphine (249 μL) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (252 mg) at room temperature and the mixture was stirred overnight. The  
35 reaction solution was concentrated. The residue was subjected



to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran  
5 (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained  
10 colorless oil was recrystallized from ethyl acetate-hexane to give 3-[3-(3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)-1-phenyl-1H-pyrazol-5-yl]propanoic acid (99.5 mg, yield 38%) as colorless crystals. melting point: 126-127°C.

15     **[0232]**

**Example 112**

A mixture of ethyl 3-[2-(benzyloxy)-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (250 mg), 1N aqueous sodium  
20 hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
25 (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-(benzyloxy)-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (237 mg, yield 99%) as colorless crystals. melting point: 128-  
30 130°C.

**Example 113**

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 3-hydroxyphenylacetate (422 mg), tributylphosphine (633  
35 µL) and tetrahydrofuran (25 ml) was added 1,1'-

azodicarbonyldipiperidine (641 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were recrystallized from ethyl acetate-hexane to give [3-(3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (424 mg, yield 74%). melting point: 108-109°C.

#### **Example 114**

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 3-(2-ethoxy-4-hydroxyphenyl)propanoate (314 mg), tributylphosphine (633 µL) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (641 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-ethoxy-4-(3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-

yl}propoxy)phenyl]propanoic acid (420 mg, yield 65%) as colorless crystals. melting point: 131-132°C.

**【0233】**

**Example 115**

5 To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (314 mg), tributylphosphine (633  $\mu$ L) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (641 mg) at room  
10 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance,  
15 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride  
20 solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless oil was recrystallized from ethyl acetate-hexane to give 3-[4-(3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]propanoic acid (423 mg, yield 68%) as colorless crystals. melting point: 125-126°C.

25 **Example 116**

To a mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-hydroxyphenyl]propanoate (300 mg), isopropanol (49.5  $\mu$ L), tributylphosphine (294  $\mu$ L) and tetrahydrofuran (15 ml) was  
30 added 1,1'-azodicarbonyldipiperidine (298 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane  
35 (1:6, volume ratio). A mixture of the obtained oily substance,

1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate  
5 layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-isopropoxyphenyl]propanoic acid (76.0  
10 mg, yield 25%) as colorless crystals. melting point: 104-105°C.

#### Example 117

To a mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-  
15 hydroxyphenyl]propanoate (400 mg), propanol (119 µL), tributylphosphine (393 µL) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (399 mg) at room temperature and the mixture was stirred for 2.5 days. The reaction solution was concentrated. The residue was subjected  
20 to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room  
25 temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-  
30 [4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-propoxyphenyl]propanoic acid (259 mg, yield 63%) as colorless crystals. melting point: 126-127°C.

【0234】

#### Example 118

35 To a mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-

(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-hydroxyphenyl]propanoate (470 mg), butanol (170  $\mu$ L), tributylphosphine (461  $\mu$ L) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (467 mg) at room  
5 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained oily substance,  
10 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride  
15 solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-butoxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (235 mg, yield 47%) as colorless crystals. melting point: 123-124°C.

#### 20 **Example 119**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (463 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-5-yl)acetate (250 mg), tributylphosphine (728  $\mu$ L) and tetrahydrofuran (30 ml) was  
25 added 1,1'-azodicarbonyldipiperidine (764 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl  
30 acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate.  
35 The ethyl acetate layer was washed with saturated aqueous

sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained pale-yellow crystals were recrystallized from ethyl acetate-hexane to give [3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-5-yl]acetic acid (255 mg, yield 39%) as colorless crystals. melting point: 151-152°C.

#### **Example 120**

To a mixture of {3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (250 mg), methyl 3-(4-hydroxy-2-methoxyphenyl)propionate (180 mg), triphenylphosphine (280 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (460 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-methoxy-4-({3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxy)phenyl]propionic acid (210 mg, yield 53%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 153-154°C.

**[0235]**

#### **Example 121**

To a mixture of {3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (410 mg), ethyl 3-(4-hydroxy-2-methylphenyl)propionate (300 mg), triphenylphosphine (450 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (750 mg) of diethyl azodicarboxylate in toluene at

room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-methyl-4-({3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxy)phenyl]propionic acid (460 mg, yield 72%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 129-130°C.

#### **Example 122**

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methanol (220 mg), methyl 3-(4-hydroxy-2-methoxyphenyl)propionate (180 mg), triphenylphosphine (260 mg) and tetrahydrofuran (10 ml) was dropwise added a 40% solution (450 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-methoxy-4-({3-methyl-1-[5-

(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxy)phenyl]propionic acid (220 mg, yield 59%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 158-159°C.

5 **Example 123**

To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methanol (380 mg), ethyl 3-(4-hydroxy-2-methylphenyl)propionate (300 mg), triphenylphosphine (450 mg) and tetrahydrofuran (10 ml) was dropwise added a 40%  
10 solution (450 mg) of diethyl azodicarboxylate in toluene at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane  
15 (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was  
20 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-methyl-4-({3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxy)phenyl]propionic acid (380 mg, yield 63%). The  
25 crystals were recrystallized from ethyl acetate-hexane. melting point: 144-145°C.

[0236]

**Example 124**

To a mixture of 3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 3-hydroxyphenylacetate (200 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
30 azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was  
35 concentrated. The residue was subjected to silica gel column



chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol  
5 (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected  
10 by filtration to give [3-(3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (520 mg, yield 94%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 132-133°C.

#### **Example 125**

15 To a mixture of 3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (420 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (320 mg), tributylphosphine (500 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room  
20 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,  
25 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
30 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-phenyl-3-(3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propionic acid (640 mg, yield 94%). The crystals were recrystallized from ethyl acetate-hexane. melting point:  
35 175-176°C.

### Example 126

To a mixture of 3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (420 mg), methyl 3-(2-ethoxy-4-hydroxyphenyl)propionate (330 mg), tributylphosphine  
5 (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a  
10 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted  
15 with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-ethoxy-4-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-  
20 yl}propoxy)phenyl]propionic acid (510 mg, yield 73%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 129-130°C.

【0237】

### Example 127

25 To a mixture of 3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 3-hydroxyphenylacetate (240 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the  
30 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
35 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol

(5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (550 mg, yield 93%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 96-97°C.

**Example 128**

To a mixture of 3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (420 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (390 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1-phenyl-1H-pyrazol-5-yl]propionic acid (700 mg, yield 95%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 125-126°C.

**Example 129**

To a mixture of 3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (420 mg), ethyl 3-(4-hydroxy-3-methoxyphenyl)propionate (330 mg), tributylphosphine

(600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-methoxy-4-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (510 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 136-137°C.

[0238]

#### Example 130

To a mixture of 3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (420 mg), ethyl [2-(3-hydroxyphenoxy)-2-methyl]propionate (340 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[3-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenoxy]propionic acid (520 mg, yield 76%). The  
5 crystals were recrystallized from ethyl acetate-hexane. melting point: 107-108°C.

#### Example 131

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (460 mg), ethyl 3-  
10 hydroxy-4-methoxyphenylacetate (310 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column  
15 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N  
20 hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-  
25 2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-methoxyphenyl]acetic acid (560 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 142-143°C.

#### Example 132

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 2-  
30 hydroxy-5-methoxyphenylacetate (250 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was  
35 concentrated. The residue was subjected to silica gel column

chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol  
5 (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected  
10 by filtration to give [2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-5-methoxyphenyl]acetic acid (560 mg, yield 92%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 138-139°C.

**[0239]**

**15 Example 133**

To a mixture of 3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl [2-(3-hydroxyphenoxy)-2-methyl]propionate (260 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was  
20 added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane  
25 (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was  
30 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[3-(3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenoxy]propionic acid (540 mg, yield 80%). The  
35 crystals were recrystallized from ethyl acetate-hexane.

melting point: 141-142°C.

#### **Example 134**

To a mixture of 3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 2-hydroxyphenylacetate (240 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (510 mg, yield 74%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 133-134°C.

#### **Example 135**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (220 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for

5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
5 collected by filtration to give [3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid (440 mg, yield 76%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 115-116°C.

10     **[0240]**

**Example 136**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-hydroxy-1-phenyl-1H-pyrazol-4-yl)acetate (300 mg),  
15 tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
20 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture  
25 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1-  
30 phenyl-1H-pyrazol-4-yl]acetic acid (580 mg, yield 89%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 117-118°C.

**Example 137**

To a mixture of methyl {2-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]phenyl}acetate (550 mg), 2-chloro-5-



(trifluoromethyl)pyridine (300 mg) and N,N-dimethylformamide (5 ml) was added sodium hydride (60%, in oil, 70 mg) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into dilute hydrochloric acid, and  
5 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume  
10 ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was  
15 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(4-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (100 mg, yield 13%). The crystals  
20 were recrystallized from ethyl acetate-hexane. melting point: 109-110°C.

#### **Example 138**

A mixture of methyl {2-[4-(3-ethoxy-1H-pyrazol-4-yl)butoxy]phenyl}acetate (1.52 g), 4-  
25 (trifluoromethyl)phenylboric acid (1.74 g), copper(II) acetate (1.25 g), pyridine (0.67 ml) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 3 days. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was  
30 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous  
35 sodium hydroxide solution (10 ml), tetrahydrofuran (10 ml) and

methanol (10 ml) was stirred at room temperature for 1 hour. 1N Hydrochloric acid (10 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
5 (MgSO<sub>4</sub>) and concentrated. A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (4 ml) and methanol (5 ml) was stirred at room temperature for 30 minutes. After concentration, water (15 ml) was added. A solution of calcium chloride (350 mg) in water (5 ml) was  
10 slowly added while stirring the mixture at room temperature. The obtained colorless amorphous was removed by filtration to give calcium [2-(4-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)butoxy)phenyl]acetate (830 mg, yield 38%).

【0241】

15 **Example 139**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 5-chloro-2-hydroxyphenylacetate (260 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
20 azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
25 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with  
30 saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [5-chloro-2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (580 mg, yield 94%). The  
35 crystals were recrystallized from ethyl acetate-hexane.

melting point: 130-131°C.

#### Example 140

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(2-hydroxy-5-methoxyphenyl)propionate (290 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-5-methoxyphenyl]propionic acid (470 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 104-105°C.

#### Example 141

To a mixture of 3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 2-hydroxyphenylacetate (240 mg), tributylphosphine (580 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (720 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol

(5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (410 mg, yield 70%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 128-129°C.

10    **[0242]**

**Example 142**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), methyl 2-hydroxy-4-methoxyphenylacetate (190 mg), tributylphosphine 15 (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a 20 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted 25 with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-methoxyphenyl]acetic 30 acid (310 mg, yield 68%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 147-148°C.

**Example 143**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), ethyl 3-(2- 35 hydroxy-4-methoxyphenyl)propionate (220 mg), tributylphosphine

(400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-methoxyphenyl]propionic acid (340 mg, yield 73%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 115-116°C.

#### Example 144

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), methyl 3-(2-hydroxyphenyl)propionate (180 mg), tributylphosphine (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected

by filtration to give 3-[2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propionic acid (360 mg, yield 82%). The crystals were recrystallized from ethyl acetate-hexane.  
5 melting point: 93-94°C.

【0243】

#### Example 145

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), ethyl 3-(2-  
10 hydroxy-3-methoxyphenyl)propionate (220 mg), tributylphosphine (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column  
15 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N  
20 hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-  
25 methoxyphenyl]propionic acid (360 mg, yield 77%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 87-88°C.

#### Example 146

30 To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), methyl 2-hydroxy-3-methoxyphenylacetate (200 mg), tributylphosphine (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the  
35 mixture was stirred overnight. The reaction solution was

concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
5 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and  
10 concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (190 mg, yield 42%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 122-123°C.

15 **Example 147**

To a mixture of {3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (300 mg), methyl 3-hydroxyphenylacetate (190 mg), tributylphosphine (430 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
20 azodicarbonyldipiperidine (550 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
25 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with  
30 saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-({3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxy)phenyl]acetic acid (340 mg, yield 77%). The crystals were recrystallized from ethyl  
35 acetate-hexane. melting point: 77-78°C.

【0244】

**Example 148**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (300 mg), ethyl 3-(2-  
5 hydroxy-6-methoxyphenyl)propionate (220 mg), tributylphosphine (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (510 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column  
10 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N  
15 hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-(3-{3-ethoxy-1-[5-  
20 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-6-methoxyphenyl]propionic acid (170 mg, yield 36%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 110-111°C.

**Example 149**

25 To a mixture of {3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (300 mg), methyl 3-hydroxyphenylacetate (250 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the  
30 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
35 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol



(5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-({3-methyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxy)phenyl]acetic acid (330 mg, yield 72%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 142-143°C.

**Example 150**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (310 mg), tributylphosphine (530 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]propanoic acid (440 mg, yield 69%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 131-132°C.

**[0245]**

**Example 151**

A mixture of methyl 3-[2-ethoxy-4-(3-{3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-

yl}propoxy)phenyl]propanoate (500 mg), 1N aqueous sodium hydroxide solution (3 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and concentrated. 1N Hydrochloric acid (3 ml) was added and the  
5 obtained colorless crystals were collected by filtration, washed with water and acetonitrile and dried to give 3-[2-ethoxy-4-(3-{3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (470 mg, yield 97%). melting point: 192-194°C.

10 **Example 152**

To a mixture of methyl 3-[2-ethoxy-4-(3-{3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (600 mg), methyl iodide (0.11 ml) and N,N-dimethylformamide (6 ml) was added sodium hydride  
15 (60%, in oil, 58 mg) at 0°C and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was  
20 subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room  
25 temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to  
30 give 3-[2-ethoxy-4-(3-{3-methoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (350 mg, yield 58%). The crystals were recrystallized from isopropyl ether. melting point: 145-146°C.

**Example 153**

35 To a mixture of methyl 3-[2-ethoxy-4-(3-{3-hydroxy-1-[5-

(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propanoate (600 mg), 1-iodopropane (0.14 ml) and N,N-dimethylformamide (6 ml) was added sodium hydride (60%, in oil, 58 mg) at 0°C and the mixture was stirred  
5 overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and  
10 colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml)  
15 was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-ethoxy-4-(3-{3-propoxy-1-[5-(trifluoromethyl)-2-  
20 pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propanoic acid (380 mg, yield 60%). The crystals were recrystallized from isopropyl ether. melting point: 112-113°C.

【0246】

#### Example 154

25 To a mixture of methyl 3-[2-ethoxy-4-(3-{3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propanoate (600 mg), 2-propanol (0.15 ml), triphenylphosphine (480 mg) and tetrahydrofuran (10 ml) was added diisopropyl azodicarboxylate (370 mg) at room  
30 temperature and the mixture was stirred for 3 hours. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). A mixture of the obtained crystals, 1N  
35 aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4

ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
5 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[2-ethoxy-4-(3-{3-isopropoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (520 mg, yield 82%). The crystals were recrystallized from isopropyl ether. melting  
10 point: 128-129°C.

#### **Example 155**

To a mixture of methyl 3-[2-ethoxy-4-(3-{3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (600 mg), 1-iodobutane (0.17 ml)  
15 and N,N-dimethylformamide (6 ml) was added sodium hydride (60%, in oil, 58 mg) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium  
20 chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5  
25 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The  
30 obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-butoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-ethoxyphenyl]propanoic acid (320 mg, yield 49%). The crystals were recrystallized from isopropyl ether. melting point: 102-103°C.

#### **Example 156**

A mixture of methyl 3-[4-(3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-ethoxyphenyl]propanoate (600 mg), 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-ethoxyphenyl]propanoic acid (380 mg, yield 65%). The crystals were recrystallized from isopropyl ether. melting point: 106-107°C.

15    **[0247]**

**Example 157**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 2-(4-hydroxyphenyl)-2-methylpropanoate (370 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 4N aqueous sodium hydroxide solution (1 ml) and methanol (10 ml) was refluxed for 15 hours. After cooling, 1N Hydrochloric acid (5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[4-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (250 mg, yield 54%). The crystals were recrystallized from hexane.

melting point: 84-85°C.

#### Example 158

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 2-(4-hydroxyphenyl)-2-methylpropanoate (360 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 4N aqueous sodium hydroxide solution (1 ml) and methanol (10 ml) was refluxed for 15 hours. After cooling, 1N hydrochloric acid (5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated to give 2-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]-2-methylpropanoic acid (410 mg, yield 84%) as a yellow oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.40 (3H, t, J=7.1 Hz), 1.58 (6H, s), 2.08 (2H, quintet, J=7.3 Hz), 2.60 (2H, t, J=7.4 Hz), 3.99 (2H, t, J=6.2 Hz), 4.34 (2H, q, J=7.1 Hz), 6.84-6.89 (2H, m), 7.28-7.33 (2H, m), 7.81 (1H, d, J=8.8 Hz), 7.90 (1H, dd, J=8.7, 2.3 Hz), 8.19 (1H, s), 8.54-8.56 (1H, m).

#### Example 159

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 2-(3-hydroxyphenyl)-2-methylpropanoate (370 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

A mixture of the obtained oily substance, 4N aqueous sodium hydroxide solution (1 ml) and methanol (10 ml) was refluxed for 15 hours. After cooling, 1N hydrochloric acid (5 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-methyl-2-[3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (320 mg, yield 42%). The crystals were recrystallized from hexane. melting point: 82-83°C.

**[0248]**

**Example 160**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 2-(3-hydroxyphenyl)-2-methylpropanoate (370 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) To a mixture of was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 4N aqueous sodium hydroxide solution (1 ml) and methanol (10 ml) was refluxed for 15 hours. After cooling, 1N hydrochloric acid (5 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 2-[3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]-2-methylpropanoic acid (420 mg, yield 87%). The crystals were recrystallized from hexane. melting point: 131-132°C.

**Example 161**

A mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoate (500 mg), 1N aqueous sodium hydroxide solution (3 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (3 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoic acid (330 mg, yield 75%). The crystals were recrystallized from isopropyl ether. melting point: 124-125°C.

**Example 162**

A mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoate (500 mg), potassium carbonate (160 mg), iodoethane (0.3 ml) and N,N-dimethylformamide (8 ml) was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-ethoxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (370



mg, yield 75%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 114-115°C.

**[0249]**

**Example 163**

5 A mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoate (500 mg), potassium carbonate (160 mg), 1-iodopropane (0.2 ml) and N,N-dimethylformamide (8 ml) was stirred overnight at room temperature. The reaction  
10 mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a  
15 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was  
20 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-propoxyphenyl]propanoic acid (440 mg, yield 86%). The crystals  
25 were recrystallized from isopropyl ether-hexane. melting point: 106-107°C.

**Example 164**

To a mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoate (200 mg), 2-propanol (0.11 ml), tributylphosphine (400 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (500 mg) at room  
30 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected  
35

to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 15 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-isopropoxyphenyl]propanoic acid (320 mg, yield 62%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 93-94°C.

**Example 165**

A mixture of ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoate (500 mg), potassium carbonate (160 mg), 1-iodobutane (0.3 ml) and N,N-dimethylformamide (8 ml) was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and colorless crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained crystals, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-butoxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-

yl)propoxy)phenyl]propanoic acid (450 mg, yield 86%). The crystals were recrystallized from isopropyl ether-hexane. melting point: 92-93°C.

[0250]

5 **Example 166**

A mixture of ethyl 3-[3-benzyloxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propanoate (665 mg), 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol  
10 (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
15 collected by filtration to give 3-[3-benzyloxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]propanoic acid (460 mg, yield 71%). The crystals were recrystallized from isopropyl ether. melting point: 115-116°C.

20 **Example 167**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl]-1-propanol (500 mg), ethyl 3-(3-hydroxy-5-methoxyphenyl)propanoate (380 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
25 azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
30 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was  
35 washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[5-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]propanoic acid (430 mg, yield 55%). The crystals  
5 were recrystallized from isopropyl ether-hexane. melting point: 99-100°C.

#### Example 168

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-  
10 hydroxy-5-methoxyphenylacetate (345 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column  
15 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N  
20 Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [5-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-  
25 methoxyphenyl]acetic acid (370 mg, yield 49%). The crystals were recrystallized from isopropyl ether. melting point: 125-126°C.

【0251】

#### 30 Example 169

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-  
hydroxy-5-methoxyphenylacetate (345 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
35 azodicarbonyldipiperidine (810 mg) at room temperature and the

mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
5 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
10 washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (410 mg, yield 54%). The  
15 crystals were recrystallized from isopropyl ether. melting point: 139-140°C.

#### Example 170

To a mixture of 3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (9.04 g), methyl 3-(2-  
20 ethoxy-4-hydroxyphenyl)propanoate (6.42 g), triphenylphosphine (7.51 g) and tetrahydrofuran (150 ml) was added diisopropyl azodicarboxylate (5.79 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography,  
25 and was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio), methyl 3-[4-(3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-ethoxyphenyl]propanoate (13.03 g, yield 94%) as a pale-yellow oily substance.

30  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.39 (3H, t,  $J=7.0$  Hz), 2.08 (2H, quintet,  $J=7.2$  Hz), 2.55-2.66 (4H, m), 2.86 (2H, t,  $J=7.7$  Hz), 3.65 (3H, s), 3.93-4.00 (4H, m), 5.35 (2H, s), 6.35 (1H, dd,  $J=8.3$ , 2.4 Hz), 6.40 (1H, d,  $J=2.4$  Hz), 7.00 (1H, d,  $J=8.3$  Hz), 7.31-7.49 (5H, m), 7.84 (1H, d,  $J=8.8$  Hz), 7.91-7.95 (1H, m), 8.22  
35 (1H, s), 8.55-8.57 (1H, m).

### Example 171

A mixture of methyl 3-[4-(3-{3-benzyloxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-ethoxyphenyl]propanoate (12.67 g), 5% palladium-carbon (1.3 g) and ethanol (150 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated to give methyl 3-[2-ethoxy-4-(3-{3-hydroxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate as colorless crystals. melting point: 147-148°C.

【0252】

### Example 172

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (3.00 g), ethyl 3-(3-benzyloxy-4-hydroxyphenyl)propanoate (2.90 g), tributylphosphine (3.84 g) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (4.80 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[3-benzyloxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (4.14 g, yield 73%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.22 (3H, t, J=7.1 Hz), 1.40 (3H, t, J=7.1 Hz), 2.13 (2H, quintet, J=6.9 Hz), 2.57 (2H, t, J=7.8 Hz), 2.64 (2H, t, J=7.4 Hz), 2.86 (2H, t, J=7.8 Hz), 4.07 (2H, t, J=6.3 Hz), 4.11 (2H, q, J=7.1 Hz), 4.35 (2H, q, J=7.1 Hz), 5.11 (2H, s), 6.68 (1H, dd, J=8.2, 1.8 Hz), 6.76 (1H, d, J=2.0 Hz), 6.84 (1H, d, J=8.1 Hz), 7.27-7.47 (5H, m), 7.80 (1H, d, J=8.8 Hz), 7.90 (1H, dd, J=8.7, 2.3 Hz), 8.19 (1H, s), 8.53-8.55 (1H, m).

### Example 173

A mixture of ethyl 3-[3-benzyloxy-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-

yl}propoxy)phenyl]propanoate (4.14 g), 5% palladium-carbon (0.4 g), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-hydroxyphenyl]propanoate (3.25 g, yield 92%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-chloroform (1:20, volume ratio). melting point: 92-93°C.

#### Example 174

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (2.69 g), ethyl 3-[2-(benzyloxy)-4-hydroxyphenyl]propanoate (2.56 g), tributylphosphine (4.24 ml) and tetrahydrofuran (180 ml) was added 1,1'-azodicarbonyldipiperidine (4.29 g) at room temperature and the mixture was stirred for 3 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and ethyl 3-[2-(benzyloxy)-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (2.79 g, yield 55%) was obtained as a white solid from a fraction eluted with ethyl acetate-hexane (1:6, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane, colorless crystal. melting point: 80-81°C.

[0253]

#### Example 175

A mixture of ethyl 3-[2-(benzyloxy)-4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (2.44 g), 5% palladium-carbon (1.00 g), tetrahydrofuran (25 ml) and ethanol (50 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated to give ethyl 3-[4-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-2-

hydroxyphenyl]propanoate (1.63 g, yield 79%) as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.23 (3H, t, J = 6.9 Hz), 1.41 (3H, t, J = 6.9 Hz), 2.01 - 2.12 (2H, m), 2.54 - 2.62 (2H, m), 2.64 - 2.71 (2H, m), 2.77 - 2.84 (2H, m), 3.92 - 3.98 (2H, m), 4.14 (2H, q, J = 6.9 Hz), 4.34 (2H, q, J = 6.9 Hz), 6.40 - 6.48 (2H, m), 6.94 (1H, d, J = 8.1 Hz), 7.50 (1H, s), 7.80 (1H, d, J = 8.7 Hz), 7.86 - 7.92 (1H, m), 8.17 (1H, s), 8.52 - 8.54 (1H, m).

【0254】

#### 10 **Example 176**

To a mixture of {3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (400 mg), methyl (3-hydroxyphenyl)acetate (300 mg), tributylphosphine (570 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (720 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxyphenylacetic acid (380 mg, yield 65%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 114-115°C.

#### **Example 177**

35 To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-



pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (6-hydroxy-2-methoxyphenyl)acetate (260 mg), tributylphosphine (540 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [6-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-methoxyphenyl]acetic acid (490 mg, yield 80%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 150-151°C.

#### Example 178

To a mixture of {3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methanol (400 mg), methyl (3-hydroxyphenyl)acetate (350 mg), tributylphosphine (570 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (720 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,

1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-({3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methoxy)phenyl]acetic acid (360 mg, yield 61%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 92-93°C.

【0255】

#### Example 179

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (380 mg), methyl (2-hydroxyphenyl)acetate (210 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (440 mg, yield 81%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 132-133°C.

### Example 180

To a mixture of 4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-butanol (430 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (260 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(4-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}butoxy)-3-methoxyphenyl]acetic acid (550 mg, yield 85%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 144-145°C.

### Example 181

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (260 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was

obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (460 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 142-143°C.

【0256】

**Example 182**

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxyphenyl)acetate (230 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-ethoxy-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic

acid (430 mg, yield 76%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 114-115°C.

#### Example 183

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-hydroxy-4-methoxyphenyl)acetate (260 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-methoxyphenyl]acetic acid (590 mg, yield 97%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 122-123°C.

#### Example 184

To a mixture of 3-{3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (450 mg), methyl (2-hydroxyphenyl)acetate (250 mg), tributylphosphine (590 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and

the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (560 mg, yield 87%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 89-90°C.

15     **[0257]**

**Example 185**

To a mixture of 3-{3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (330 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to

give [2-(3-{3-isopropyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (730 mg, yield 96%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 114-115°C.

5 **Example 186**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (380 mg), methyl (2-fluoro-3-hydroxyphenyl)acetate (240 mg), tributylphosphine (490 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
10 azodicarbonyldipiperidine (620 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to  
15 silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for  
20 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-2-fluorophenyl]acetic acid (430 mg, yield 76%). The crystals  
25 were recrystallized from ethyl acetate-hexane. melting point: 120-121°C.

**Example 187**

30 To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (380 mg), methyl (3-hydroxyphenyl)acetate (200 mg), tributylphosphine (490 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
azodicarbonyldipiperidine (610 mg) at room temperature and the  
35 mixture was stirred overnight. The reaction solution was

concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
5 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture  
10 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-({3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxy)phenyl]acetic acid (480 mg, yield 89%). The  
15 crystals were recrystallized from ethyl acetate-hexane. melting point: 129-130°C.

**[0258]**

**Example 188**

20 To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (430 mg), methyl (2-hydroxyphenyl)acetate (230 mg), tributylphosphine (530 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (670 mg) at room temperature and the  
25 mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
30 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture  
35 was extracted with ethyl acetate. The ethyl acetate layer was



washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-({3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxy}phenyl]acetic acid (310 mg, yield 51%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 131-132°C.

#### Example 189

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(3-hydroxy-1-phenyl-1H-pyrazol-5-yl)propionate (300 mg), tributylphosphine (470 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (590 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1-phenyl-1H-pyrazol-5-yl]propionic acid (190 mg, yield 30%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 182-183°C.

#### Example 190

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (400 mg), methyl (3-hydroxy-4-methoxyphenyl)acetate (250 mg), tributylphosphine (530 mg)

and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (660 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the  
5 residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,  
10 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
15 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-({3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methoxy-4-methoxy)phenyl]acetic acid (240 mg, yield 40%). The crystals were recrystallized from ethyl acetate-hexane. melting point:  
20 145-146°C.

**[0259]**

#### **Example 191**

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)methanol (400 mg), methyl 3-(3-  
25 hydroxyphenyl)propionate (230 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) To a mixture of was added 1,1'-azodicarbonyldipiperidine (660 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the  
30 residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,  
35 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran

(5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
5 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxyphenyl)propionic acid (300 mg, yield 52%). The crystals were recrystallized from ethyl acetate-hexane.  
10 melting point: 94-95°C.

#### **Example 192**

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (400 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-5-yl)propionate (250 mg),  
15 tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed  
20 by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml),  
25 tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The  
30 obtained colorless crystals were collected by filtration to give 3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxy-1-methyl-1H-pyrazol-5-yl)propionic acid (380 mg, yield 65%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 162-163°C.

#### **Example 193**

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (400 mg), ethyl 3-(3-hydroxy-1-methyl-1H-pyrazol-4-yl)propionate (250 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was  
5 added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue  
10 was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room  
15 temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to  
20 give 3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxy-1-methyl-1H-pyrazol-4-yl)propionic acid (410 mg, yield 70%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 143-144°C.

【0260】

25 **Example 194**

To a mixture of 3-{3-(1-methylethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (270 mg), tributylphosphine (510 mg) and tetrahydrofuran (30  
30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane  
35 (1:2, volume ratio). A mixture of the obtained oily substance,

1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
5 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-2-(3-{3-(1-methylethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazole-2-yl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (130 mg, yield  
10 22%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 144-145.

#### Example 195

To a mixture of {3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methanol (400 mg), ethyl 4-(3-  
15 hydroxyphenyl)butanoate (260 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the  
20 residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,  
25 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and ethanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
30 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 4-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}methoxyphenyl)butanoic acid (390 mg, yield 65%). The crystals were recrystallized from ethyl acetate-hexane.  
35 melting point: 128-129°C.

### Example 196

To a mixture of 3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (240 mg), tributylphosphine  
5 (470 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (590 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and  
10 the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran  
15 (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
20 collected by filtration to give [3-methoxy-2-(3-{3-phenyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenylacetic acid (290 mg, yield 50%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 134-135°C.

25     【0261】

### Example 197

To a mixture of 3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (250 mg), tributylphosphine  
30 (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and  
35 the filtrate was concentrated. The residue was subjected to

silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran  
5 (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
10 collected by filtration to give [2-(3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (420 mg, yield 70%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 121-122°C.

15 **Example 198**

To a mixture of 3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxyphenyl)acetate (210 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
20 azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to  
25 silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for  
30 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-butyl-1-[5-  
35 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-

yl}propoxy)phenyl]acetic acid (420 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 106-107°C.

#### **Example 199**

5 To a mixture of 3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (350 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (190 mg), tributylphosphine (450 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room  
10 temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a  
15 colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was  
20 added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-  
25 pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid (420 mg, yield 84%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 125-126°C.

**[0262]**

#### **Example 200**

30 To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (4-ethoxy-3-hydroxyphenyl)acetate (340 mg), tributylphosphine (650 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (810 mg) at room temperature and the  
35 mixture was stirred overnight. The reaction solution was



concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
5 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture  
10 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [4-ethoxy-3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (580 mg, yield 74%). The  
15 crystals were recrystallized from ethyl acetate-hexane. melting point: 116-117°C.

#### Example 201

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (4-ethoxy-3-hydroxyphenyl)acetate (250 mg), tributylphosphine (460 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (580 mg) at room temperature and the mixture was stirred overnight. The reaction solution was  
25 concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane  
30 (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was  
35 washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-ethoxyphenyl]acetic acid (510 mg, yield 85%). The crystals  
5 were recrystallized from ethyl acetate-hexane. melting point: 134-135°C.

#### Example 202

To a mixture of 3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (4-  
10 ethoxy-3-hydroxyphenyl)acetate (260 mg), tributylphosphine (510 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the  
15 residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,  
20 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
25 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-ethoxyphenyl]acetic acid (510 mg, yield 83%). The crystals were recrystallized from ethyl acetate-hexane. melting point:  
30 105-106°C.

【0263】

#### Example 203

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (5-  
35 hydroxy-3-methoxyphenyl)acetate (260 mg), tributylphosphine

(550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-5-methoxyphenyl]acetic acid (530 mg, yield 87%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 109-110°C.

#### Example 204

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (4-ethoxy-3-hydroxyphenyl)acetate (270 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for

5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were collected by filtration to give [4-ethoxy-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (540 mg, yield 86%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 124-125°C.

#### 10 **Example 205**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-4-methoxyphenyl)acetate (260 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-methoxyphenyl]acetic acid (460 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 143-144°C.

**[0264]**

#### 35 **Example 206**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-5-methoxyphenyl)acetate (270 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
5 azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to  
10 silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for  
15 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[5-  
20 (trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-5-methoxyphenyl]acetic acid (460 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 143-144°C.

#### Example 207

25 To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-fluoro-2-hydroxyphenyl)acetate (240 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
azodicarbonyldipiperidine (690 mg) at room temperature and the  
30 mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
35 obtained from a fraction eluted with ethyl acetate-hexane

(1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture  
5 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-fluoro-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (560 mg, yield 94%). The  
10 crystals were recrystallized from ethyl acetate-hexane. melting point: 140-141°C.

#### Example 208

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (6-hydroxy-2-methoxyphenyl)acetate (260 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was  
15 concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane  
20 (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was  
25 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-6-methoxyphenyl]acetic acid (460 mg, yield 75%). The crystals  
30 were recrystallized from ethyl acetate-hexane. melting point:

183-184°C.

**[0265]**

**Example 209**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl 5-hydroxy-2-methoxyphenylacetate (260 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [5-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy))-2-methoxyphenyl]acetic acid (510 mg, yield 84%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 127-128°C.

**Example 210**

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-fluoro-2-hydroxyphenyl)acetate (220 mg), tributylphosphine (460 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (580 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and

the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,  
5 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
10 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-fluorophenyl]acetic acid (520 mg, yield 91%). The crystals were recrystallized from ethyl acetate-hexane. melting point:  
15 149-150°C.

#### Example 211

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-fluoro-2-hydroxyphenyl)acetate (240 mg), tributylphosphine  
20 (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and  
25 the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran  
30 (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
35 collected by filtration to give [3-fluoro-2-(3-{3-propyl-1-[5-



(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (510 mg, yield 86%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 105-106°C.

5     **【0266】**

**Example 212**

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (240 mg),  
10     tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed  
15     by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml),  
20     tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The  
25     obtained colorless crystals were collected by filtration to give [2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (510 mg, yield 86%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 100-101°C.

30     **Example 213**

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methylphenyl)acetate (220 mg),  
tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was  
35     added 1,1'-azodicarbonyldipiperidine (600 mg) at room

temperature and the mixture was stirred overnight at 50°C. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue  
5 was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room  
10 temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to  
15 give [2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-methylphenyl]acetic acid (430 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 125-126°C.

#### **Example 214**

20 To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-fluoro-2-hydroxyphenyl)acetate (220 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room  
25 temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a  
30 colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was  
35 added. The mixture was extracted with ethyl acetate. The

ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-3-fluorophenyl]acetic acid (390 mg, yield 60%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 102-103°C.

【0267】

#### Example 215

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxyphenyl)acetate (200 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (370 mg, yield 66%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 65-66°C.

#### Example 216

To a mixture of 3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400

mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (250 mg), tributylphosphine (500 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight. The  
5 reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a  
10 colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The  
15 ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-2-(3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (510 mg, yield 85%). The  
20 crystals were recrystallized from ethyl acetate-hexane. melting point: 117-118°C.

#### **Example 217**

To a mixture of 3-{1-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl}-1-propanol (500 mg),  
25 methyl (2-hydroxy-3-methoxyphenyl)acetate (300 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (750 mg) at room temperature and the mixture was stirred overnight. The  
30 reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl  
35 acetate-hexane (1:4, volume ratio). A mixture of the obtained

oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The  
5 ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{1-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid  
10 (610 mg, yield 83%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 96-97°C.

【0268】

#### Example 218

To a mixture of 3-[1-(5-bromo-2-pyridyl)-3-isopropyl-1H-  
15 pyrazol-4-yl]-1-propanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (310 mg), tributylphosphine (630 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (790 mg) at room temperature and the mixture was stirred overnight. The reaction solution was  
20 concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
25 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture  
30 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-bromo-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (720 mg, yield 95%). The crystals were recrystallized  
35 from ethyl acetate-hexane. melting point: 152-153°C.

### Example 219

To a mixture of 3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methylphenyl)acetate (230 mg),  
5 tributylphosphine (500 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (630 mg) at room temperature and the mixture was stirred overnight at 50°C. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed  
10 by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml),  
15 tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The  
20 obtained colorless crystals were collected by filtration to give [3-methyl-2-(3-{3-(1-methylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (380 mg, yield 66%). The crystals were recrystallized from ethyl acetate-hexane.  
25 melting point: 134-135°C.

### Example 220

To a mixture of 3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (240 mg),  
30 tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed  
35 by filtration and the filtrate was concentrated. The residue

was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml),  
5 tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The  
10 obtained colorless crystals were collected by filtration to give [3-methoxy-2-(3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (480 mg, yield 81%). The crystals were recrystallized from ethyl acetate-hexane.  
15 melting point: 107-108°C.

**[0269]**

**Example 221**

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400  
20 mg), methyl (3-ethoxy-2-hydroxyphenyl)acetate (250 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml)  
25 was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained  
30 oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium  
35 chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The

obtained colorless crystals were collected by filtration to give [3-ethoxy-2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (540 mg, yield 89%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 83-84°C.

#### Example 222

To a mixture of 3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methylphenyl)acetate (210 mg), tributylphosphine (480 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (600 mg) at room temperature and the mixture was stirred overnight at 50°C. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methyl-2-(3-{3-(1-methylbutyl)-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (360 mg, yield 63%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 147-148°C.

#### Example 223

To a mixture of 3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (670 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (430 mg), tributylphosphine (910 mg) and tetrahydrofuran (40 ml) was added 1,1'-azodicarbonyldipiperidine (1.15 g) at room temperature and the



mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (40 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to  
5 silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for  
10 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-chloro-2-pyridyl)-  
15 3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (760 mg, yield 74%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 85-86°C.

【0270】

20 **Example 224**

To a mixture of 3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (500 mg), methyl (2-hydroxy-3-methylphenyl)acetate (300 mg), tributylphosphine (660 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
25 azodicarbonyldipiperidine (820 mg) at room temperature and the mixture was stirred overnight at 50°C. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to  
30 silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for  
35 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture

was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-methylphenyl)acetic acid (280 mg, yield 46%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 106-107°C.

#### Example 225

To a mixture of 3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]-1-propanol (500 mg), methyl (3-ethoxy-2-hydroxyphenyl)acetate (350 mg), tributylphosphine (660 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (820 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-chloro-2-pyridyl)-3-(1-ethylpropyl)-1H-pyrazol-4-yl]propoxy}-3-ethoxyphenyl)acetic acid (590 mg, yield 75%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 92-93°C.

#### Example 226

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (380 mg), methyl (3-

ethyl-2-hydroxyphenyl)acetate (240 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution  
5 was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio), methyl [3-  
10 ethyl-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (400 mg, yield 68%) as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.23 (3H, t, J=6.8 Hz), 1.35 (6H, d, J=6.8 Hz), 2.12-2.17 (2H, m), 2.67 (2H, q, J=6.8 Hz), 2.74 (2H, t, J=8.4  
15 Hz), 3.00-3.10 (1H, m), 3.68 (2H, s), 3.68 (3H, s), 3.87 (2H, t, J=6.4 Hz), 7.04 (1H, t, J=7.6 Hz), 7.10 (1H, dd, J=7.6, 2.0 Hz), 7.15 (1H, dd, J=7.6, 2.0 Hz), 7.94-7.97 (1H, m), 8.04 (1H, d, J=8.8 Hz), 8.33 (1H, s), 8.60-8.61 (1H, m).

【0271】

#### 20 **Example 227**

A mixture of methyl [3-ethyl-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (400 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol  
25 (5 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected  
30 by filtration to give [3-ethyl-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (370 mg, yield 96%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 155-156°C.

#### 35 **Example 228**

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (380 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (240 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
5 azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel  
10 column chromatography, and methyl [3-ethyl-2-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetate (490 mg, yield 83%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).  
15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.03 (3H, t, J=7.2 Hz), 1.23 (3H, t, J=7.6 Hz), 1.73-1.80 (2H, m), 2.11-2.17 (2H, m), 2.64-2.73 (6H, m), 3.68 (2H, s), 3.68 (3H, s), 3.86 (2H, t, J=6.4 Hz), 7.04 (1H, t, J=7.6 Hz), 7.11 (1H, dd, J=7.6, 2.0 Hz), 7.15 (1H, dd, J=7.6, 2.0 Hz), 7.96 (1H, dd, J=8.8, 2.0 Hz), 8.02 (1H, d, J=8.8 Hz), 8.34 (1H, s), 8.61 (1H, m).

#### Example 229

A mixture of methyl [3-ethyl-2-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetate (490 mg), 1N aqueous sodium  
25 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and  
30 concentrated. The obtained colorless crystals were collected by filtration to give [3-ethyl-2-(3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (450 mg, yield 96%). The crystals were recrystallized from hexane-ethyl acetate.  
35 melting point: 146-147°C

【0272】

**Example 230**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (570 mg), methyl (3-cyano-2-hydroxyphenyl)acetate (360 mg), tributylphosphine (790 mg) and tetrahydrofuran (40 ml) was added 1,1'-azodicarbonyldipiperidine (980 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-cyano-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (680 mg, yield 75%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.35 (6H, d, J=7.2 Hz), 2.14-2.21 (2H, m), 2.72-2.76 (2H, m), 3.03-3.09 (1H, m), 3.69 (2H, s), 3.69 (3H, s), 4.32 (2H, t, J=6.0 Hz), 7.13 (1H, t, J=7.6 Hz), 7.48 (1H, dd, J=7.6, 1.6 Hz), 7.54 (1H, dd, J=7.6, 1.6 Hz), 7.95 (1H, dd, J=8.4, 2.8 Hz), 8.04 (1H, d, J=8.4 Hz), 8.33 (1H, s), 8.60-8.61 (1H, m).

**Example 231**

A mixture of methyl [3-cyano-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (650 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-cyano-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (590 mg, yield 95%). The

crystals were recrystallized from hexane-ethyl acetate.

melting point: 144-145°C

#### **Example 232**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (320 mg), methyl (3-cyano-2-hydroxyphenyl)acetate (200 mg), tributylphosphine (440 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (550 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-cyano-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (360 mg, yield 71%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.03 (3H, t, J=7.6 Hz), 1.72-1.80 (2H, m), 2.12-2.19 (2H, m), 2.65 (2H, t, J=8.0 Hz), 2.72 (2H, t, J=8.4 Hz), 3.69 (2H, s), 3.70 (3H, s), 4.31 (2H, t, J=6.0 Hz), 7.13 (1H, t, J=8.0 Hz), 7.48 (1H, dd, J=8.0, 1.6 Hz), 7.53 (1H, dd, J=8.0, 1.6 Hz), 7.96 (1H, dd, J=8.4, 2.0 Hz), 8.02 (1H, d, J=8.4 Hz), 8.34 (1H, s), 8.61-8.62 (1H, m).

【0273】

#### **Example 233**

A mixture of methyl [3-cyano-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (330 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-cyano-2-(3-{3-propyl-1-[5-

(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (270 mg, yield 86%). The crystals were recrystallized from hexane-ethyl acetate: melting point: 146-147°C

5 **Example 234**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (570 mg), methyl (3-bromo-2-hydroxyphenyl)acetate (460 mg), tributylphosphine (790 mg) and tetrahydrofuran (40 ml) was added 1,1'-  
10 azodicarbonyldipiperidine (980 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel  
15 column chromatography, and methyl [3-bromo-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetate (750 mg, yield 76%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).  
20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.35 (6H, d, J=6.8 Hz), 2.14-2.21 (2H, m), 2.76 (2H, t, J=8.4 Hz), 2.60-3.10 (1H,m), 3.69 (3H, s), 3.71 (2H, s), 4.04 (2H, t, J=6.4 Hz), 6.97 (1H, t, J=8.0 Hz), 7.22 (1H, dd, J=8.0, 1.6 Hz), 7.48 (1H, dd, J=8.0,1.6 Hz), 7.95 (1H, dd, J=8.8,2.0 Hz), 8.04 (1H, d, J=8.8 Hz), 8.34 (1H, s), 8.60-8.61  
25 (1H, m).

**Example 235**

A mixture of methyl [3-bromo-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetate (700 mg), 1N aqueous sodium  
30 hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and  
35 concentrated. The obtained colorless crystals were collected

by filtration to give [3-bromo-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (610 mg, yield 89%). The crystals were recrystallized from hexane-ethyl acetate.

5 melting point: 146-147°C

【0274】

#### Example 236

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (430 mg), methyl (3-bromo-2-hydroxyphenyl)acetate (340 mg), tributylphosphine (590 mg) and tetrahydrofuran (40 ml) was added 1,1'-azodicarbonyldipiperidine (730 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-bromo-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (570 mg, yield 78%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.03 (3H, t, J=7.6 Hz), 1.72-1.80 (2H, m), 2.12-2.20 (2H, m), 2.66 (2H, t, J=8.0 Hz), 2.73 (2H, t, J=8.4 Hz), 3.69 (3H, s), 3.70 (2H, s), 4.03 (2H, t, J=6.4 Hz), 6.97 (1H, t, J=7.6 Hz), 7.22 (1H, dd, J=7.6, 1.6 Hz), 7.48 (1H, dd, J=7.6, 1.6 Hz), 7.96 (1H, dd, J=8.8, 2.0 Hz), 8.02 (1H, d, J=8.8 Hz), 8.34 (1H, s), 8.61-8.62 (1H, m).

#### Example 237

A mixture of methyl [3-bromo-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (500 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature 4 hours and 1N hydrochloric acid (5 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with



saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-bromo-2-(3-{3-propyl-1-[5-

5 yl)propoxy)phenyl]acetic acid (380 mg, yield 78%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 145-146°C

#### Example 238

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-  
10 pyridinyl]-1H-pyrazol-4-yl}-1-propanol (430 mg), methyl (3-chloro-2-hydroxyphenyl)acetate (280 mg), tributylphosphine (580 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (730 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution  
15 was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-chloro-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-  
20 yl)propoxy)phenyl]acetate (590 mg, yield 85%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.35 (6H, d, J=6.8 Hz), 2.11-2.30 (2H, m), 2.74 (2H, t, J=8.0 Hz), 3.04-3.10 (1H, m), 3.69 (3H, s), 3.70 (2H, s), 4.06 (2H, t, J=6.4 Hz), 7.02 (1H, t, J=8.0 Hz), 7.17 (1H, dd, J=8.0, 1.6 Hz), 7.31 (1H, dd, J=8.0, 1.6 Hz), 7.95 (1H, dd, J=8.8, 2.0 Hz), 8.04 (1H, d, J=8.8 Hz), 8.33 (1H, s), 8.60-8.61 (1H, m).

【0275】

#### 30 Example 239

A mixture of methyl [3-chloro-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetate (510 mg), 1N aqueous sodium hydroxide solution (5 ml), tetrahydrofuran (5 ml) and methanol  
35 (5 ml) was stirred at room temperature for 4 hours. 1N

Hydrochloric acid (5 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-chloro-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (400 mg, yield 81%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 141-142°C

**Example 240**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (460 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (270 mg), tributylphosphine (580 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (730 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-ethyl-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (510 mg, yield 73%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.89 (6H, t, J=7.2 Hz), 1.24 (3H, t, J=7.6 Hz), 1.60-1.88 (4H, m), 2.09-2.16 (2H, m), 2.50-2.72 (5H, m), 3.69 (2H, s), 3.69 (3H, s), 3.87 (2H, t, J=6.0 Hz), 7.04 (1H, t, J=7.6 Hz), 7.11 (1H, dd, J=7.6, 2.0 Hz), 7.15 (1H, dd, J=7.6, 2.0 Hz), 7.95 (1H, dd, J=8.8, 2.4 Hz), 8.04 (1H, d, J=8.8 Hz), 8.33 (1H, s), 8.61 (1H, m).

**Example 241**

A mixture of methyl [3-ethyl-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetate (480 mg), 1N aqueous sodium hydroxide solution (7 ml), tetrahydrofuran (5 ml) and methanol

(5 ml) was stirred at room temperature 4 hours and 1N hydrochloric acid (7 ml) was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-ethyl-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (350 mg, yield 75%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 130-131°C

【0276】

#### Example 242

To a mixture of 3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (70 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (50 mg), tributylphosphine (110 mg) and tetrahydrofuran (10 ml) was added 1,1'-azodicarbonyldipiperidine (140 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetate (80 mg, yield 69%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.24 (3H, t, J=7.6 Hz), 1.34 (6H, d, J=6.8 Hz), 2.05-2.20 (2H, m), 2.56-2.80 (4H, m), 3.04-3.10 (1H, m), 3.68 (2H, s), 3.68 (3H, s), 3.86 (2H, t, J=6.4 Hz), 7.04 (1H, t, J=7.6 Hz), 7.05-7.16 (2H, m), 7.71 (1H, dd, J=8.8, 2.8 Hz), 7.90 (1H, dd, J=8.8, 0.8 Hz), 8.24 (1H, s), 8.29 (1H, m).

#### Example 243

A mixture of methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetate (80 mg), 1N aqueous sodium hydroxide solution (2 ml),

tetrahydrofuran (2 ml) and methanol (2 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium  
5 chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetic acid (50 mg, yield 62%). The crystals were recrystallized from hexane-ethyl acetate.  
10 melting point: 142-143°C.

#### Example 244

To a mixture of 3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (300 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (190 mg),  
15 tributylphosphine (410 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (520 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and  
20 the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [3-ethyl-2-(3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl]propoxy)phenyl]acetate (250 mg, yield 53%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-  
25 hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.24 (3H, t, J=7.6 Hz), 1.35 (6H, d, J=6.8 Hz), 2.10-2.19 (2H, m), 2.65-2.72 (2H, m), 2.77 (2H, t, J=8.0 Hz), 3.05-3.11 (1H, m), 3.68 (2H, s), 3.69 (3H, s), 3.89 (2H, t, J=6.0 Hz), 7.05 (1H, t, J=7.6 Hz), 7.11 (1H, dd, J=7.6, 1.6  
30 Hz), 7.15 (1H, dd, J=7.6, 1.6 Hz), 7.84 (1H, d, J=9.2 Hz), 8.30 (1H, d, J=9.2 Hz), 8.55 (1H, s).

【0277】

#### Example 245

A mixture of methyl [3-ethyl-2-(3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-

35

yl]propoxy)phenyl]acetate (220 mg), 1N aqueous sodium hydroxide solution (7 ml), tetrahydrofuran (5 ml) and methanol (5 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (7 ml) was added, and the mixture was  
5 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-ethyl-2-(3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-  
10 yl]propoxy)phenyl]acetic acid (140 mg, yield 67%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 126-127°C.

#### Example 246

To a mixture of 3-[1-(5-bromo-2-pyridinyl)-3-isopropyl-  
15 1H-pyrazol-4-yl]-1-propanol (250 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (150 mg), tributylphosphine (330 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (410 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution  
20 was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl (2-{3-[1-(5-bromo-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-  
25 ethylphenyl)acetate (210 mg, yield 54%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.24 (3H, t, J=7.6 Hz), 1.34 (6H, d, J=7.2 Hz), 2.05-2.17 (2H, m), 2.64-2.74 (4H, m), 3.02-3.09 (1H, m),  
30 3.68 (2H, s), 3.68 (3H, s), 3.86 (2H, t, J=6.4 Hz), 7.04 (1H, t, J=7.6 Hz), 7.10 (1H, dd, J=7.6, 1.6 Hz), 7.15 (1H, dd, J=7.6, 1.6 Hz), 7.84-7.85 (2H, m), 8.24 (1H, s), 8.38-8.39 (1H, m).

#### Example 247

35 A mixture of methyl (2-{3-[1-(5-bromo-2-pyridinyl)-3-

isopropyl-1H-pyrazol-4-yl]propoxy)-3-ethylphenyl)acetate (190 mg), 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (2 ml) and methanol (2 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (2 ml) was added  
5 and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-bromo-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetic acid (140 mg, yield 76%). The  
10 crystals were recrystallized from hexane-ethyl acetate. melting point: 152°C.

**[0278]**

**Example 248**

15 To a mixture of 3-{1-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]-3-isopropyl-1H-pyrazol-4-yl}-1-propanol (250 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (140 mg), tributylphosphine (310 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (390 mg) at room  
20 temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl [2-(3-{1-[3-  
25 chloro-5-(trifluoromethyl)-2-pyridinyl]-3-isopropyl-1H-pyrazol-4-yl}propoxy)-3-ethylphenyl]acetate (180 mg, yield 48%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.24 (3H, t, J=7.6 Hz), 1.37 (6H, d, J=7.2  
30 Hz), 2.02-2.18 (2H, m), 2.64-2.77 (4H, m), 3.06-3.12 (1H, m), 3.68 (2H, s), 3.68 (3H, s), 3.88 (2H, t, J=6.4 Hz), 7.05 (1H, t, J=7.6 Hz), 7.10-7.12 (1H, m), 7.15 (1H, dd, J=7.6, 2.0 Hz), 8.08 (2H, m), 8.62 (1H, m).

**Example 249**

35 A mixture of methyl [2-(3-{1-[3-chloro-5-

(trifluoromethyl)-2-pyridinyl]-3-isopropyl-1H-pyrazol-4-yl]propoxy)-3-ethylphenyl]acetate (160 mg), 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (2 ml) and methanol (2 ml) was stirred at room temperature for 4 hours. 1N  
5 Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{1-[3-chloro-5-  
10 (trifluoromethyl)-2-pyridinyl]-3-isopropyl-1H-pyrazol-4-yl]propoxy)-3-ethylphenyl]acetic acid (90 mg, yield 58%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 93-95°C.

#### Example 250

15 To a mixture of 3-[1-(3,5-dichloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (250 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (160 mg), tributylphosphine (340 mg) and tetrahydrofuran (20 ml) was added 1,1'-azodicarbonyldipiperidine (430 mg) at room temperature and the  
20 mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel column chromatography, and methyl (2-{3-[1-(3,5-dichloro-2-  
25 pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetate (260 mg, yield 67%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.23 (3H, t, J=7.6 Hz), 1.36 (6H, d, J=6.8  
30 Hz), 2.10-2.16 (2H, m), 2.67 (2H, q, J=7.6 Hz), 2.74 (2H, t, J=8.4 Hz), 3.06-3.13 (1H, m), 3.68 (2H, s), 3.68 (3H, s), 3.87 (2H, t, J=6.4 Hz), 7.04 (1H, t, J=7.6 Hz), 7.11 (1H, dd, J=7.6, 1.6 Hz), 7.15 (1H, dd, J=7.6, 1.6 Hz), 7.87 (1H, d, J=2.4 Hz), 7.89 (1H, s), 8.35-8.36 (1H, m).

35 【0279】

### Example 251

A mixture of methyl (2-{3-[1-(3,5-dichloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetate (230 mg), 1N aqueous sodium hydroxide solution (3 ml),  
5 tetrahydrofuran (3 ml) and methanol (3 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (3 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The  
10 obtained colorless crystals were collected by filtration to give (2-{3-[1-(3,5-dichloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetic acid (180 mg, yield 81%). The crystals were recrystallized from hexane-ethyl acetate. melting point: 93-95°C.

### 15 Example 252

To a mixture of 3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (530 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (340 mg), tributylphosphine (740 mg) and tetrahydrofuran (30 ml) was added 1,1'-  
20 azodicarbonyldipiperidine (920 mg) at room temperature and the mixture was stirred overnight at 65°C. The reaction solution was concentrated and isopropyl ether was added. The insoluble material was removed by filtration and the filtrate was concentrated. Then, the residue was subjected to silica gel  
25 column chromatography, and methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetate (440 mg, yield 53%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio).

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.88 (6H, t, J=7.6 Hz), 1.23 (3H, t, J=7.6 Hz), 1.70-1.79 (4H, m), 2.10-2.13 (2H, m), 2.55-2.71 (5H, m), 3.68 (2H, s), 3.68 (3H, s), 3.86 (2H, t, J=6.4 Hz), 7.04 (1H, t, J=7.6 Hz), 7.12 (1H, dd, J=7.6, 2.0 Hz), 7.15 (1H, dd, J=7.6, 2.0 Hz), 7.70 (1H, dd, J=8.8, 2.4 Hz), 7.89 (1H, dd,  
35 J=8.8, 0.4 Hz), 8.24 (1H, s), 8.29-8.30 (1H, m).



### Example 253

A mixture of methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetate (440 mg), 1N aqueous sodium hydroxide solution (3 ml),  
5 tetrahydrofuran (3 ml) and methanol (3 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (3 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The  
10 obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-ethylphenyl)acetic acid (300 mg, yield 70%). The crystals were recrystallized from hexane-ethyl acetate.  
melting point: 114-115°C

15 [0280]

### Example 254

To a solution of 4-propyl-3-(3-{4-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazole (400 mg) in N,N-dimethylformamide (6 ml) was added  
20 sodium hydride (60%, in oil, 46 mg) at 0°C and the mixture was stirred at room temperature for 15 minutes. Bromomethyl acetate (0.10 ml) was added at 0°C and the mixture was stirred at room temperature for 1 hour. The reaction mixture was  
25 poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and white crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained  
30 crystal, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium  
35 chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The

obtained colorless crystals were collected by filtration to give [4-propyl-3-(3-{4-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-1-yl]acetic acid (310 mg, yield 69%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 138-139.

#### Example 255

To a solution of 3-(3-{4-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-propyl-1H-pyrazole (400 mg) in N,N-dimethylformamide (6 ml) was added sodium hydride (60%, in oil, 46 mg) at 0°C and the mixture was stirred at room temperature for 15 minutes. Bromomethyl acetate (0.10 ml) was added at 0°C and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and white crystals were obtained from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio). A mixture of the obtained crystal, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-(3-{4-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-4-propyl-1H-pyrazol-1-yl]acetic acid (330 mg, yield 72%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 134-135.

#### Example 256

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), ethyl 3-(1-cyclohexyl-3-hydroxy-1H-pyrazol-5-yl)propanoate (370 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was

added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
5 obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture  
10 was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-cyclohexyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propanoic acid (240 mg, yield  
15 35%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 164-165.

【0281】

#### Example 257

20 To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(1-cyclohexyl-3-hydroxy-1H-pyrazol-5-yl)propanoate (370 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room  
25 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance,  
30 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
35 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were

collected by filtration to give 3-[1-cyclohexyl-3-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propanoic acid (270 mg, yield 40%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 89-90.

#### Example 258

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (230 mg), ethyl (2-fluoro-3-hydroxyphenyl)acetate (140 mg), tributylphosphine (280 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (350 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-fluoro-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (220 mg, yield 68%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 109-110.

#### Example 259

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (310 mg), tributylphosphine (640 mg) and tetrahydrofuran (35 ml) was added 1,1'-azodicarbonyldipiperidine (800 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column

chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2.5 ml), tetrahydrofuran (4 ml) and  
5 methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
10 collected by filtration to give [3-methoxy-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (590 mg, yield 78%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 122-123.

15     **[0282]**

**Example 260**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (620 mg), methyl (3-ethoxy-2-hydroxyphenyl)acetate (420 mg), tributylphosphine  
20 (800 mg) and tetrahydrofuran (35 ml) was added 1,1'-azodicarbonyldipiperidine (1.00 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a  
25 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (3 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (3 ml) was added, and the mixture was  
30 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-ethoxy-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (880 mg, yield 90%). The  
35

crystals were recrystallized from ethyl acetate-hexane.  
melting point: 133-134.

**Example 261**

To a mixture of 3-{3-cyclopropyl-1-[5-(trifluoromethyl)-  
5 2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(1-cyclohexyl-3-hydroxy-1H-pyrazol-5-yl)propanoate (300 mg), tributylphosphine (460 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred overnight. The  
10 reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran  
15 (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
20 collected by filtration to give 3-[1-cyclohexyl-3-(3-{3-cyclopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propanoic acid (300 mg, yield 46%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 190-191.

25 **Example 262**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(1-cyclohexyl-3-hydroxy-1H-pyrazol-5-yl)propanoate (340 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was  
30 added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane  
35 (1:4, volume ratio). A mixture of the obtained oily substance,

1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-cyclohexyl-3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propanoic acid (230 mg, yield 34%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 166-167.

【0283】

#### Example 263

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}-1-propanol (350 mg), ethyl 3-[3-hydroxy-1-isopropyl-1H-pyrazol-5-yl]propanoate (250 mg), tributylphosphine (440 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (560 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[1-isopropyl-3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]propanoic acid (200 mg, yield 36%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 130-131.

#### Example 264

A mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (390 mg), 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours, and concentrated. To a mixture of the obtained residue and water (10 ml) was added a solution of calcium chloride (0.20 g) in water (1 ml) at room temperature and the mixture was stirred overnight. The resulting white precipitates were collected by filtration to give calcium (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (300 mg, yield 81%) as amorphous.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.23 (6H, d, J=6.6 Hz), 1.85-1.98 (2H, m), 2.60 (2H, t, J=7.4 Hz), 2.96 (1H, septet, J=6.9 Hz), 3.37 (2H, s), 3.73 (3H, s), 3.91 (2H, t, J=6.2 Hz), 5.29 (2H, br s), 6.75-6.90 (3H, m), 7.08 (1H, dd, J=8.6, 2.9 Hz), 7.51 (1H, d, J=8.4 Hz), 7.72 (1H, d, J=2.4 Hz), 8.10 (1H, s).

#### Example 265

To a mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (390 mg) and N,N-dimethylformamide (6 ml) was added acetic anhydride (0.10 ml) at room temperature and the mixture was stirred overnight. Water (20 ml) was added to the reaction mixture and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with aqueous sodium hydrogen carbonate, dried (MgSO<sub>4</sub>), and concentrated. A mixture of the obtained residue, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-acetylamino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (320 mg,



yield 78%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 158-159.

【0284】

#### Example 266

5 To a mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (400 mg) and N,N-dimethylformamide (6 ml) was added propionyl chloride (0.12 ml) at 0°C and the mixture was stirred at room temperature overnight. Water (20 ml) was added to the reaction  
10 mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with aqueous sodium hydrogen carbonate, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-  
15 hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl  
20 acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (3-methoxy-2-{3-[3-isopropyl-1-(5-propanoylamino-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetic acid (340 mg,  
25 yield 78%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 147-148.

#### Example 267

To a mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate  
30 (400 mg) and N,N-dimethylformamide (6 ml) was added butyryl chloride (0.14 ml) at 0°C and the mixture was stirred at room temperature overnight. Water (20 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with aqueous sodium hydrogen  
35 carbonate, dried (MgSO<sub>4</sub>) and concentrated. The residue was

subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml),  
5 tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The  
10 obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-butyrylamino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (350 mg, yield 83%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 119-120.

15 **Example 268**

To a mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (400 mg) and N,N-dimethylformamide (6 ml) was added isobutyryl chloride (0.15 ml) at 0°C and the mixture was stirred at room  
20 temperature overnight. Water (20 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with aqueous sodium hydrogen carbonate, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless  
25 oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added  
30 and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-2-(3-{3-isopropyl-1-[5-(2-methylpropanoylamino)-2-pyridyl]-1H-pyrazol-4-

35

yl]propoxy)phenyl]acetic acid (370 mg, yield 82%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 122-123.

【0285】

5 **Example 269**

To a mixture of methyl (2-{3-[1-(5-amino-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (400 mg), pyridine (0.10 ml) and acetonitrile (6 ml) was added methanesulfonyl chloride (0.10 ml) at 0°C, and the mixture was  
10 stirred at room temperature for 1 hour. Water (15 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column  
15 chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N  
20 Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (3-methoxy-2-{3-[3-isopropyl-  
25 1-(5-methylsulfonylamino-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetic acid (270 mg, yield 58%). The crystals were recrystallized from ethanol. melting point: 176-177.

**Example 270**

30 A mixture of methyl (3-methoxy-2-{3-[3-isopropyl-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetate (400 mg), 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) at room temperature 5 hours was stirred. 1N Hydrochloric acid (1.5 ml) was added,  
35 and the mixture was extracted with ethyl acetate. The ethyl

acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (3-methoxy-2-{3-[3-isopropyl-1-(5-nitro-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetic acid (240 mg, yield 62%).  
The crystals were recrystallized from ethanol. melting point: 161-162.

#### Example 271

To a mixture of 6-[4-(3-hydroxypropyl)-3-isopropyl-1H-pyrazol-1-yl]pyridine-3-carbonitrile (520 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (380 mg), tributylphosphine (780 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (970 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and (2-{3-[1-(5-cyano-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (460 mg, yield 67%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (3:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 144-145.

【0286】

#### Example 272

To a mixture of 3-[3-isopropyl-1-(5-methyl-2-pyridyl)-1H-pyrazol-4-yl]-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (300 mg), tributylphosphine (620 mg) and

tetrahydrofuran (50 ml) was added 1,1'-  
azodicarbonyldipiperidine (780 mg) at room temperature and the  
mixture was stirred overnight. The reaction solution was  
concentrated. The residue was subjected to silica gel column  
5 chromatography, and a colorless oil was obtained from a  
fraction eluted with ethyl acetate-hexane (1:3, volume ratio).  
A mixture of the obtained oily substance, 1N aqueous sodium  
hydroxide solution (2.5 ml), tetrahydrofuran (4 ml) and  
methanol (4 ml) was stirred at room temperature for 5 hours.  
10 1N Hydrochloric acid (2.5 ml) was added, and the mixture was  
extracted with ethyl acetate. The ethyl acetate layer was  
washed with saturated aqueous sodium chloride solution, dried  
(MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
collected by filtration to give (3-methoxy-2-{3-[3-isopropyl-  
15 1-(5-methyl-2-pyridyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetic  
acid (470 mg, yield 72%). The crystals were recrystallized  
from ethyl acetate-hexane. melting point: 132-133.

#### **Example 273**

To a mixture of 3-[1-(5-fluoro-2-pyridyl)-3-isopropyl-1H-  
20 pyrazol-4-yl]-1-propanol (500 mg), methyl (2-hydroxy-3-  
methoxyphenyl)acetate (410 mg), tributylphosphine (770 mg) and  
tetrahydrofuran (50 ml) was added 1,1'-  
azodicarbonyldipiperidine (960 mg) at room temperature and the  
mixture was stirred overnight. The reaction solution was  
25 concentrated. The residue was subjected to silica gel column  
chromatography, and a colorless oil was obtained from a  
fraction eluted with ethyl acetate-hexane (1:4, volume ratio).  
A mixture of the obtained oily substance, 1N aqueous sodium  
hydroxide solution (2.5 ml), tetrahydrofuran (4 ml) and  
30 methanol (4 ml) was stirred at room temperature for 5 hours.  
1N Hydrochloric acid (2.5 ml) was added, and the mixture was  
extracted with ethyl acetate. The ethyl acetate layer was  
washed with saturated aqueous sodium chloride solution, dried  
(MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were  
35 collected by filtration to give (2-{3-[1-(5-fluoro-2-pyridyl)-

3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (180 mg, yield 22%). The crystals were recrystallized from ethanol-hexane. melting point: 125-126.

#### Example 274

5 To a mixture of 3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (280 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room  
10 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance,  
15 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
20 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-2-(3-{3-isopropyl-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (490 mg, yield 80%). The crystals were recrystallized from ethanol-hexane. melting  
25 point: 92-93.

【0287】

#### Example 275

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}-1-propanol  
30 (400 mg), benzyl (2-hydroxy-3-methoxyphenyl)acetate (450 mg), tributylphosphine (520 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (640 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected  
35 to silica gel column chromatography, and a colorless oil was

obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 5% palladium-carbon (0.1 g) and tetrahydrofuran (8 ml) was stirred overnight at room temperature under a hydrogen  
5 atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and [3-methoxy-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (390 mg, yield 65%) was obtained  
10 as colorless crystals from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 131-132.

#### Example 276

15 To a mixture of 3-[1-(5-ethylpyrimidin-2-yl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (310 mg), tributylphosphine (590 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (740 mg) at room temperature and the  
20 mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium  
25 hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
30 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(5-ethylpyrimidin-2-yl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (430 mg, yield 68%). The crystals were recrystallized from ethyl acetate-hexane. melting point:  
35 103-104.

### Example 277

To a mixture of 3-[1-(6-methoxypyridazin-3-yl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (300 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (240 mg), tributylphosphine (440 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (550 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give (3-methoxy-2-{3-[1-(6-methoxypyridazin-3-yl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}phenyl)acetic acid (400 mg, yield 84%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 124-125.

【0288】

### Example 278

To a mixture of 3-{1-[5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl (4-hydroxy-3-methoxyphenyl)acetate (280 mg), tributylphosphine (520 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and



methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
5 (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-methoxy-4-(3-{1-[5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (250 mg, yield 41%). The crystals were recrystallized from ethyl acetate-hexane.  
10 melting point: 134-135.

#### **Example 279**

To a mixture of 3-{1-[5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (300 mg), tributylphosphine  
15 (520 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (650 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a  
20 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (1.5 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (1.5 ml) was added, and the mixture was  
25 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give 3-[3-methoxy-4-(3-{1-[5-(trifluoromethyl)-2-pyridyl]-3-isopropyl-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (220 mg, yield 35%). The  
30 crystals were recrystallized from ethyl acetate-hexane. melting point: 118-119.

#### **Example 280**

To a mixture of 6-[4-(3-hydroxypropyl)-3-isopropyl-1H-pyrazol-1-yl]pyridazine-3-carbonitrile (400 mg), methyl (2-

hydroxy-3-methoxyphenyl)acetate (320 mg), tributylphosphine (600 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (740 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 2 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and 6-(4-{3-[2-methoxy-6-(methoxycarbonylmethyl)phenoxy]propyl}-3-isopropyl-1H-pyrazol-1-yl)pyridazine-3-carboxylic acid (220 mg, yield 32%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 146-147.

【0289】

#### Example 281

To a mixture of 3-[3-isopropyl-1-(5-chloro-2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (400 mg), methyl (2-hydroxyphenyl)acetate (261 mg), tributylphosphine (713  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (722 mg) at room temperature and the mixture was stirred for 2.5 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}phenyl)acetate (470 mg, yield 77%) was obtained as a pale-yellow oily substance from a fraction eluted with ethyl acetate-hexane (1:12, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.32 (6H, d, J = 6.9 Hz), 2.02 - 2.18 (2H, m), 2.62 - 2.71 (2H, m), 2.95 - 3.10 (1H, m), 3.65 (2H, s), 3.67 (3H, s), 4.00 - 4.06 (2H, m), 6.80 - 6.94 (2H, m), 7.15 - 7.27 (2H, m), 7.69 (1H, dd, J = 2.7, 9.0 Hz), 7.88 (1H, d, J = 9.0 Hz), 8.19 (1H, s), 8.27 (1H, d, J = 2.7 Hz).

#### Example 282

To a mixture of 3-[3-isopropyl-1-(5-chloro-2-pyridinyl)-1H-pyrazol-4-yl]-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (308 mg), tributylphosphine (713 μL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (722 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (550 mg, yield 84%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:12, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.33 (6H, d, J = 6.9 Hz), 2.01 - 2.12 (2H, m), 2.64 - 2.72 (2H, m), 2.97 - 3.12 (1H, m), 3.66 (3H, s), 3.68 (2H, s), 3.83 (3H, s), 4.02 - 4.09 (2H, m), 6.78 - 6.86 (2H, m), 6.96 - 7.03 (1H, m), 7.68 (1H, dd, J = 2.7, 9.0 Hz), 7.88 (1H, d, J = 9.0 Hz), 8.23 (1H, s), 8.27 (1H, d, J = 2.7 Hz).

#### Example 283

To a mixture of 3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (367 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-5-yl)acetate (200 mg), tributylphosphine (588 μL) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (596 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained

oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. 5 The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained pale-red solid was recrystallized from ethyl acetate to give [1-methyl-3-(3-{3-methyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-5-yl]acetic 10 acid (222 mg, yield 44%) as colorless crystals. melting point: 143-144°C.

**[0290]**

**Example 284**

To a mixture of 2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-ethanol (356 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-5-yl)acetate (200 mg), tributylphosphine (588 µL) and tetrahydrofuran (25 ml) was added 1,1'-azodicarbonyldipiperidine (596 mg) at room temperature and the mixture was stirred overnight. The 20 reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), 25 tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The 30 residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (7:3, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give [3-(2-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethoxy)-1-methyl-1H-pyrazol-5-yl]acetic acid (104 mg, yield 35

20%) as colorless crystals. melting point: 156-158°C.

**Example 285**

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl 3-(2-ethoxy-4-hydroxyphenyl)propanoate (392 mg), tributylphosphine (792  $\mu$ L) and tetrahydrofuran (32 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give methyl 3-[2-ethoxy-4-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoate (174 mg, yield 34%) as colorless crystals. melting point: 79-81°C.

**Example 286**

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (3-hydroxyphenyl)acetate (529 mg), tributylphosphine (792  $\mu$ L) and tetrahydrofuran (32 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (524 mg, yield 73%) as colorless

crystals. melting point: 128-130°C.

【0291】

**Example 287**

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(3-ethoxy-4-hydroxyphenyl)propanoate (393 mg), tributylphosphine (792  $\mu$ L) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[4-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]propanoic acid (403 mg, yield 51%) as colorless crystals. melting point: 111-112°C.

**Example 288**

To a mixture of 3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (2-hydroxyphenyl)acetate (291 mg), tributylphosphine (792  $\mu$ L) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml)

was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [2-(3-(3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenyl]acetic acid (479 mg, yield 67%) as colorless crystals. melting point: 121-122°C.

**Example 289**

To a mixture of 3-(3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl 2-(3-hydroxyphenoxy)-2-methylpropaneacetate (393 mg), tributylphosphine (792  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained oily substance was recrystallized from ethyl acetate-hexane to give 2-[3-(3-(3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)phenoxy]-2-methylpropanoic acid (140 mg, yield 18%) as colorless crystals. melting point: 98-99°C.

**[0292]**

**Example 290**

To a mixture of ethyl 2-{3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy}-2-methylpropanoate (400 mg), 2-chloro-3-(trifluoromethyl)pyridine (240 mg) and N,N-dimethylformamide (20 ml) was added sodium hydride (60%, in oil, 52.8 mg) at 0°C and the mixture was stirred at room temperature for 3 hours. Thereafter, to the reaction solution was added ethyl iodide (106  $\mu$ L), and the mixture was stirred for 2.5 hours. To the reaction solution was added saturated aqueous ammonia chloride, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. A mixture of the obtained colorless oil, 1N aqueous sodium hydroxide solution (325  $\mu$ L), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium chloride (36.0 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The resulting white precipitates were collected by filtration to give calcium 2-[3-(3-{3-ethoxy-1-[3-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-2-methylpropanoate (166 mg, yield 31%) as amorphous.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.33 (3H, t,  $J = 7.2$  Hz), 1.41 (6H, s), 1.92 - 2.04 (2H, m), 2.45 - 2.55 (2H, m), 3.88 - 3.96 (2H, m), 4.24 (2H, q,  $J = 7.2$  Hz), 6.36 - 6.45 (3H, m), 6.96 - 7.04 (1H, m), 7.44 - 7.51 (1H, m), 8.19 (1H, s), 8.29 - 8.35 (1H,



m), 8.63 - 8.68 (1H, m).

#### Example 291

A mixture of ethyl 2-[3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy]-2-methylpropanoate (400 mg), 3-  
5 (trifluoromethyl)phenylboric acid (418 mg), copper(II) acetate (300 mg), pyridine (160  $\mu$ L) and N,N-dimethylformamide (10 ml) was stirred overnight at room temperature. To the reaction solution was added saturated aqueous ammonia chloride, and the mixture was extracted with ethyl acetate. The ethyl acetate  
10 layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily  
15 substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous  
20 sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (610  $\mu$ L),  
25 tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium chloride (67.6 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The  
30 resulting white precipitates were collected by filtration to give calcium 2-[3-(3-(3-ethoxy-1-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl)propoxy)phenoxy]-2-methylpropanoate (343 mg, yield 63%) as amorphous.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.34 (3H, t,  $J = 7.0$  Hz), 1.41 (6H, s),  
35 1.90 - 2.07 (2H, m), 2.42 - 2.54 (2H, m), 3.88 - 4.00 (2H, m),

4.29 (2H, q,  $J = 7.0$  Hz), 6.36 - 6.46 (3H, m), 6.96 - 7.07 (1H, m), 7.45 - 7.53 (1H, m), 7.59 - 7.70 (1H, m), 7.95 - 8.04 (2H, m), 8.41 (1H, s).

#### Example 292

5        A mixture of ethyl 2-{3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy}-2-methylpropanoate (400 mg), 2-(trifluoromethyl)phenylboric acid (418 mg), copper(II) acetate (300 mg), pyridine (160  $\mu$ L) and N,N-dimethylformamide (10 ml) was stirred overnight at room temperature. To the reaction  
10       solution was added saturated aqueous ammonia chloride, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless  
15       oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml)  
20       was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl  
25       acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (265  $\mu$ L), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour, and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium  
30       chloride (29.3 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The resulting white precipitates were collected by filtration to give calcium 2-[3-(3-{3-ethoxy-1-[2-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)phenoxy]-2-methylpropanoate (109 mg,  
35       yield 20%) as amorphous.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.30 (3H, t, J = 7.0 Hz), 1.41 (6H, s), 1.86 - 2.04 (2H, m), 2.42 - 2.54 (2H, m), 3.86 - 3.98 (2H, m), 4.19 (2H, q, J = 7.0 Hz), 6.35 - 6.47 (3H, m), 6.96 - 7.06 (1H, m), 7.53 - 7.65 (2H, m), 7.68 - 7.90 (3H, m).

5     **【0293】**

**Example 293**

A mixture of ethyl 2-{3-[3-(3-ethoxy-1H-pyrazol-4-yl)propoxy]phenoxy}-2-methylpropanoate (400 mg), 4-ethylphenylboric acid (318 mg), copper(II) acetate (289 mg),  
10 pyridine (154 μL) and N,N-dimethylformamide (10 ml) was stirred overnight at room temperature. To the reaction solution was added saturated aqueous ammonia chloride, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
15 (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and  
20 ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica  
25 gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (600 μL), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour,  
30 and concentrated. To a mixture of the obtained residue and water (50 ml) was added calcium chloride (66.2 mg) dissolved in a small amount of water and the mixture was stirred overnight at room temperature. The resulting white precipitates were collected by filtration to give calcium 2-  
35 (3-{3-[3-ethoxy-1-(4-ethylphenyl)-1H-pyrazol-4-yl]propoxy}-

phenoxy)-2-methylpropanoate (274 mg, yield 55%) as amorphous.  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.18 (3H, t, J = 7.8 Hz), 1.33 (3H, t, J =  
7.0 Hz), 1.41 (6H, s), 1.88 - 2.06 (2H, m), 2.40 - 2.55 (2H,  
m), 2.59 (2H, q, J = 7.8 Hz), 3.86 - 3.98 (2H, m), 4.25 (2H,  
5 q, J = 7.0 Hz), 6.35 - 6.46 (3H, m), 6.95 - 7.07 (1H, m), 7.23  
(2H, d, J = 8.8 Hz), 7.57 (2H, d, J = 8.8 Hz), 8.13 (1H, s).

【0294】

#### Example 294

A mixture of ethyl 2-{3-[3-(3-ethoxy-1H-pyrazol-4-  
10 yl)propoxy]phenoxy}-2-methylpropanoate (400 mg), 4-  
methylphenylboric acid (288 mg), copper(II) acetate (289 mg),  
pyridine (154 μL) and N,N-dimethylformamide (10 ml) was stirred  
overnight at room temperature. To the reaction solution was  
added saturated aqueous ammonia chloride, and the mixture was  
15 extracted with ethyl acetate. The ethyl acetate layer was  
washed with saturated aqueous sodium chloride solution, dried  
(MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica  
gel column chromatography, and a colorless oil was obtained  
from a fraction eluted with ethyl acetate-hexane (1:8, volume  
20 ratio). A mixture of the obtained oily substance, 1N aqueous  
sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and  
ethanol (25 ml) was stirred overnight at room temperature. 1N  
Hydrochloric acid (25 ml) was added, and the mixture was  
extracted with ethyl acetate. The ethyl acetate layer was  
25 washed with saturated aqueous sodium chloride solution, dried  
(MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica  
gel column chromatography, and a colorless oil was obtained  
from a fraction eluted with ethyl acetate-hexane (1:1, volume  
ratio). A mixture of the obtained oily substance, 1N aqueous  
30 sodium hydroxide solution (775 μL), tetrahydrofuran (25 ml) and  
ethanol (25 ml) was stirred at room temperature for 1 hour,  
and concentrated. To a mixture of the obtained residue and  
water (50 ml) was added calcium chloride (86.0 mg) dissolved  
in a small amount of water and the mixture was stirred  
35 overnight at room temperature. The resulting white

precipitates were collected by filtration to give calcium 2-(3-{3-[3-ethoxy-1-(4-methylphenyl)-1H-pyrazol-4-yl]propoxy}phenoxy)-2-methylpropanoate (353 mg, yield 73%) as amorphous.

5 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.32 (3H, t, J = 7.0 Hz), 1.41 (6H, s), 1.88 - 2.04 (2H, m), 2.29 (3H, s), 2.40 - 2.53 (2H, m), 3.86 - 3.98 (2H, m), 4.25 (2H, q, J = 7.0 Hz), 6.35 - 6.47 (3H, m), 6.95 - 7.08 (1H, m), 7.21 (2H, d, J = 8.4 Hz), 7.55 (2H, d, J = 8.4 Hz), 8.13 (1H, s).

#### 10 **Example 295**

To a mixture of 4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-butanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (330 mg), tributylphosphine (762 μL) and tetrahydrofuran (120 ml) was added 1,1'-  
15 azodicarbonyldipiperidine (772 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio).  
20 A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
25 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-methoxy-2-(4-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}butoxy)phenyl]acetic acid (451 mg, yield 60%) as colorless  
30 crystals: melting point: 111-112°C.

#### **Example 296**

To a mixture of 3-{3-propyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxyphenyl)acetate (234 mg), tributylphosphine  
35 (638 μL) and tetrahydrofuran (100 ml) was added 1,1'-

azodicarbonyldipiperidine (646 mg) at room temperature and the mixture was stirred for 2 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a  
5 fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 2.5 days. 1N Hydrochloric acid (25 ml) was added, and the mixture was  
10 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and [2-(3-{3-propyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic  
15 acid (340 mg, yield 59%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:2, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.99 (3H, t, J = 7.4 Hz), 1.60 - 1.82 (2H, m), 1.91 - 2.08 (2H, m), 2.54 - 2.68 (4H, m), 3.65 (2H, s),  
20 3.90 - 4.00 (2H, m), 6.74 - 6.92 (2H, m), 7.08 - 7.26 (2H, m), 7.54 - 7.73 (5H, m).

**[0295]**

#### **Example 297**

To a mixture of 3-{3-propyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-propanol (420 mg),  
25 methyl (2-hydroxy-3-methoxyphenyl)acetate (290 mg), tributylphosphine (668 μL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (676 mg) at room temperature and the mixture was stirred overnight for 2.5  
30 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml),  
35 tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred

overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The  
5 residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio). The obtained solid was recrystallized from diisopropyl ether-hexane to give [3-methoxy-2-(3-{3-propyl-1-[4-(trifluoromethyl)phenyl]-1H-  
10 pyrazol-4-yl}propoxy)phenyl]acetic acid (472 mg, yield 74%) as colorless crystals. melting point: 95-96°C.

#### **Example 298**

A mixture of methyl 3-[2-ethoxy-4-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-  
15 yl}propoxy)phenyl]propanoate (86.3 mg), 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 8 hours. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
20 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-ethoxy-4-(3-{3-ethoxy-1-[4-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]propanoic acid (67.3 mg, yield 80%) as  
25 colorless crystals. melting point: 119-120°C.

#### **Example 299**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (240 mg),  
30 tributylphosphine (638 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (646 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was  
35 obtained from a fraction eluted with ethyl acetate-hexane

(1:3, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid (441 mg, yield 76%) as colorless crystals. melting point: 122-123°C.

**[0296]**

#### **Example 300**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-ethoxy-2-hydroxyphenyl)acetate (424 mg), tributylphosphine (638 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (646 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-ethoxy-2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (455 mg, yield 72%) as colorless crystals. melting point: 141-142°C.

#### **Example 301**



To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-ethoxy-2-hydroxyphenyl)acetate (420 mg), tributylphosphine (633  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-  
5 azodicarbonyldipiperidine (641 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A  
10 mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with  
15 saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-ethoxy-2-(3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (415 mg, yield 66%) as colorless  
20 crystals. melting point: 114-115°C.

#### Example 302

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxyphenyl)acetate (206 mg), tributylphosphine (563  $\mu$ L) and  
25 tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction  
30 eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with  
35 ethyl acetate. The ethyl acetate layer was washed with

saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [2-(3-{3-cyclohexyl-1-[5-

(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (345 mg, yield 63%) as colorless crystals. melting point: 127-128°C.

【0297】

#### Example 303

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (211 mg), tributylphosphine (563 μL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred for 3 days. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid (457 mg, yield 82%) as colorless crystals. melting point: 157-158°C.

#### Example 304

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl (3-hydroxy-4-methoxyphenyl)acetate (261 mg), tributylphosphine (563 μL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred overnight. The reaction solution was

concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:7, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-4-methoxyphenyl]acetic acid (268 mg, yield 46%) as colorless crystals. melting point: 117-118°C.

**Example 305**

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (170 mg), methyl (1-ethyl-3-hydroxy-1H-pyrazol-4-yl)acetate (100 mg), tributylphosphine (272  $\mu$ L) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (275 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (15 ml), tetrahydrofuran (15 ml) and ethanol (15 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (15 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [1-ethyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (117 mg, yield 46%) as colorless crystals. melting point: 105-106°C.

【0298】

**Example 306**

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (3-ethoxy-2-hydroxyphenyl)acetate (466 mg), tributylphosphine (703  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (712 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:12, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [2-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-ethoxyphenyl]acetic acid (537 mg, yield 72%) as colorless crystals. melting point: 156-157°C.

**Example 307**

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (243 mg), tributylphosphine (563  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:12, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric

acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from  
5 ethyl acetate-hexane to give [2-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (427 mg, yield 73%) as colorless crystals. melting point: 140-141°C.

#### Example 308

10 A mixture of methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}phenyl)acetate (230 mg), 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (20 ml) was added, and the  
15 mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-  
20 yl]propoxy}phenyl)acetic acid (182 mg, yield 82%) as colorless crystals. melting point: 141-142°C.

【0299】

#### Example 309

A mixture of methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}phenyl)acetate (240 mg), 5%  
25 palladium-carbon (100 mg) and ethanol (50 ml) was stirred at room temperature for 2 days under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel  
30 column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred overnight at room temperature. 1N  
35 Hydrochloric acid (20 ml) was added, and the mixture was

extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give (2-{3-[3-isopropyl-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy}phenyl)acetic acid (92.4 mg, yield 43%) as colorless crystals. melting point: 140-142°C.

#### **Example 310**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (354 mg), methyl 3-(3-hydroxy-1-methyl-1H-pyrazol-4-yl)propanoate (246 mg), tributylphosphine (563 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (570 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-4-yl]propanoic acid (307 mg, yield 58%) as colorless crystals. melting point: 124-125°C.

#### **Example 311**

A mixture of methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (260 mg), 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (20 ml)

was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (214 mg, yield 85%) as colorless crystals. melting point: 148-149°C.

**[0300]**

**Example 312**

A mixture of methyl (2-{3-[1-(5-chloro-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetate (290 mg), 5% palladium-carbon (300 mg) and ethanol (50 ml) was stirred overnight at room temperature under a hydrogen atmosphere. Palladium-carbon was removed by filtration and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless oil was recrystallized from diisopropyl ether-hexane to give (2-{3-[3-isopropyl-1-(2-pyridinyl)-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (82.0 mg, yield 32%) as colorless crystals. melting point: 102-104°C.

**Example 313**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (170 mg), methyl (1-ethyl-3-hydroxy-1H-pyrazol-4-yl)acetate (100 mg), tributylphosphine (272 µL) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (275 mg) at room temperature and the mixture was stirred overnight. The

reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale-yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained  
5 oily substance, 1N aqueous sodium hydroxide solution (20 ml), tetrahydrofuran (20 ml) and ethanol (20 ml) was stirred at room temperature for 4 hours. 1N Hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium  
10 chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (3:2, volume ratio) extract. The obtained solid was recrystallized from diisopropyl ether-hexane to give [1-ethyl-  
15 3-(3-(3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-1H-pyrazol-4-yl]acetic acid (105 mg, yield 42%) as colorless crystals. melting point: 99-100°C.

#### **Example 314**

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-  
20 pyridinyl]-1H-pyrazol-4-yl)-1-propanol (400 mg), methyl 3-(3-hydroxy-1-methyl-1H-pyrazol-4-yl)propanoate (278 mg), tributylphosphine (638 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (646 mg) at room temperature and the mixture was stirred overnight. The  
25 reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran  
30 (25 ml) and ethanol (25 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white  
35 solid was recrystallized from ethyl acetate-hexane to give 3-



[1-methyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]propanoic acid (436 mg, yield 73%) as colorless crystals. melting point: 103-104°C.

5     **[0301]**

**Example 315**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (313 mg), methyl (2-hydroxy-3-methylphenyl)acetate (541 mg), tributylphosphine  
10 (748 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (757 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred at said temperature for 1 hour. The reaction solution was concentrated. The residue was subjected to silica gel column  
15 chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:19, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric  
20 acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction  
25 eluted with ethyl acetate-hexane (7:13, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give [2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methylphenyl]acetic acid (135 mg, yield 29%) as colorless crystals. melting point: 159-160°C.

30     **Example 316**

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), methyl (2-hydroxy-3-methylphenyl)acetate (305 mg), tributylphosphine  
35 (703 µL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (712 mg) at room temperature and the

mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale yellow oily substance was obtained from a fraction  
5 eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was  
10 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (3:7, volume  
15 ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give [2-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methylphenyl]acetic acid (193 mg, yield 27%) as colorless crystals. melting point: 184-185°C.

#### 20 **Example 317**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (329 mg), ethyl (1-cyclohexyl-3-hydroxy-1H-pyrazol-4-yl)acetate (250 mg), tributylphosphine (523 µL) and tetrahydrofuran (100 ml) was  
25 added 1,1'-azodicarbonyldipiperidine (530 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was  
30 obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the  
35 mixture was extracted with ethyl acetate. The ethyl acetate

layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained oily substance was recrystallized from ethyl acetate-hexane to give [1-cyclohexyl-3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (145 mg, yield 27%) as colorless crystals. melting point: 116-117°C.

【0302】

#### Example 318

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (450 mg), ethyl (5-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (292 mg), tributylphosphine (716  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (727 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [5-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid (246 mg, yield 38%) as colorless crystals. melting point: 146-148°C.

#### Example 319

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-

pyridinyl]-1H-pyrazol-4-yl]-1-propanol (500 mg), methyl (2-hydroxy-3-methylphenyl)acetate (344 mg), tributylphosphine (792  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the  
5 mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale yellow solid was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of  
10 the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous  
15 sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-methyl-2-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (268 mg, yield 37%) as colorless  
20 crystals. melting point: 134-135°C.

#### **Example 320**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl]-1-propanol (400 mg), ethyl (1-cyclohexyl-3-hydroxy-1H-pyrazol-4-yl)acetate (336 mg),  
25 tributylphosphine (638  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (646 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica  
30 gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N  
35 Hydrochloric acid (25 ml) was added, and the mixture was

extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a pale yellow solid was  
5 obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give [1-cyclohexyl-3-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (453 mg, yield 68%) as  
10 colorless crystals. melting point: 127-128°C.

【0303】

#### Example 321

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl]-1-propanol (450 mg), ethyl (5-  
15 hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (291 mg), tributylphosphine (718 μL) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (727 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction  
20 solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (3:7, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran  
25 (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white  
30 solid was recrystallized from ethyl acetate-hexane to give [1-methyl-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (274 mg, yield 42%) as colorless crystals. melting point: 136-138°C.

#### Example 322

35 To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-

pyridinyl]-1H-pyrazol-4-yl]-1-propanol (500 mg), ethyl (1-ethyl-5-hydroxy-1H-pyrazol-4-yl)acetate (381 mg), tributylphosphine (797  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room  
5 temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a pale-yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane  
10 (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate  
15 layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The obtained solid was  
20 recrystallized from ethyl acetate-hexane to give [1-ethyl-5-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (187 mg, yield 25%) as colorless crystals. melting point: 120-121°C.

### Example 323

25 To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl]-1-propanol (500 mg), ethyl 3-(2-hydroxy-3-methoxyphenyl)propanoate (395 mg), tributylphosphine (797  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature and the  
30 mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the  
35 obtained oily substance, 1N aqueous sodium hydroxide solution

(25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[2-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]propanoic acid (429 mg, yield 55%) as colorless crystals. melting point: 112-113°C.

**[0304]**

**Example 324**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl 3-(3-hydroxy-4-methoxyphenyl)propanoate (395 mg), tributylphosphine (797  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give 3-[3-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-4-methoxyphenyl]propanoic acid (447 mg, yield 57%) as colorless crystals. melting point: 93-94°C.

**Example 325**

To a mixture of 3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-

pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl (5-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (286 mg), tributylphosphine (703  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (712 mg) at room  
5 temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (3:7, volume  
10 ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room temperature. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
15 washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained pale-yellow crystals were recrystallized from ethyl acetate-hexane to give [5-(3-{3-cyclohexyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1-methyl-1H-pyrazol-4-yl]acetic acid (538 mg,  
20 yield 78%) as colorless crystals. melting point: 137-138°C.

#### **Example 326**

To a mixture of 3-(3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)-1-propanol (500 mg), ethyl (1-ethyl-5-hydroxy-1H-pyrazol-4-yl)acetate (349 mg),  
25 tributylphosphine (797  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica  
30 gel column chromatography, and a yellow oily substance was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred overnight at room  
35 temperature. 1N Hydrochloric acid (25 ml) was added, and the



mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained pale-yellow crystals were recrystallized from ethyl acetate-hexane  
5 to give [1-ethyl-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (431 mg, yield 58%) as colorless crystals. melting point: 125-126°C.

【0305】

10 **Example 327**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl (5-hydroxy-4-methyl-1H-pyrazol-1-yl)acetate (240 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was  
15 added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained  
20 from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour. 1N Hydrochloric acid (25 ml) was added, and the mixture was  
25 extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and a brown solid was obtained from a fraction eluted with methanol-ethyl acetate (1:19, volume  
30 ratio). The obtained solid was recrystallized from ethyl acetate-hexane to give [5-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-4-methyl-1H-pyrazol-1-yl]acetic acid (222 mg, yield 37%) as colorless crystals. melting point: 123-124°C.

35 **Example 328**

To a mixture of 3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl (4-ethyl-5-hydroxy-1H-pyrazol-1-yl)acetate (349 mg), tributylphosphine (797  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (807 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained solid, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 30 minutes. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [4-ethyl-5-(3-{3-isopropyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-1-yl]acetic acid (635 mg, yield 85%) as colorless crystals. melting point: 111-112°C.

#### **Example 329**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl (5-hydroxy-4-methyl-1H-pyrazol-1-yl)acetate (240 mg), tributylphosphine (550 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (690 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour. 1N

Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained white solid was  
5 recrystallized from ethyl acetate-hexane to give [4-methyl-5-(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-1-yl]acetic acid (433 mg, yield 75%) as colorless crystals. melting point: 145-146°C.

**[0306]**

10 **Example 330**

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol (500 mg), ethyl (4-ethyl-5-hydroxy-1H-pyrazol-1-yl)acetate (318 mg), tributylphosphine (728 μL) and tetrahydrofuran (100  
15 ml) was added 1,1'-azodicarbonyldipiperidine (737 mg) at room temperature and the mixture was heated to 50°C. The mixture was stirred overnight at said temperature. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a yellow oily substance was  
20 obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 30 minutes. 1N Hydrochloric acid (25 ml) was added, and  
25 the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless oil was recrystallized from ethyl acetate-hexane to give [4-ethyl-5-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-  
30 pyrazol-1-yl]acetic acid (389 mg, yield 54%) as colorless crystals. melting point: 124-125°C.

**Example 331**

To a mixture of 3-{3-propyl-1-[5-(trifluoromethyl)-2-  
35 pyridinyl]-1H-pyrazol-4-yl}-1-propanol (400 mg), ethyl (4-

ethyl-5-hydroxy-1H-pyrazol-1-yl)acetate (279 mg),  
tributylphosphine (638  $\mu$ L) and tetrahydrofuran (100 ml) was  
added 1,1'-azodicarbonyldipiperidine (646 mg) at room  
temperature and the mixture was heated to 50°C. The mixture  
5 was stirred at said temperature for 8 hours. The reaction  
solution was concentrated. The residue was subjected to silica  
gel column chromatography, and a white solid was obtained from  
a fraction eluted with ethyl acetate-hexane (1:3, volume  
ratio). A mixture of the obtained solid, 1N aqueous sodium  
10 hydroxide solution (25 ml), tetrahydrofuran (25 ml) and  
ethanol (25 ml) was stirred at room temperature for 1 hour. 1N  
Hydrochloric acid (25 ml) was added, and the mixture was  
extracted with ethyl acetate. The ethyl acetate layer was  
washed with saturated aqueous sodium chloride solution, dried  
15 ( $\text{MgSO}_4$ ) and concentrated. The obtained white solid was  
recrystallized from ethyl acetate-hexane to give [4-ethyl-5-  
(3-{3-propyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-  
yl}propoxy)-1H-pyrazol-1-yl]acetic acid (420 mg, yield 71%) as  
colorless crystals. melting point: 135-136°C.

#### 20 **Example 332**

To a mixture of 1-{6-[4-(3-hydroxypropyl)-3-isopropyl-1H-  
pyrazol-1-yl]-3-pyridinyl}ethanone (320 mg), methyl (2-  
hydroxy-3-methoxyphenyl)acetate (239 mg), tributylphosphine  
(553  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-  
25 azodicarbonyldipiperidine (560 mg) at room temperature and the  
mixture was stirred for 3 hours. The reaction solution was  
concentrated. The residue was subjected to silica gel column  
chromatography, and a yellow oily substance was obtained from  
a fraction eluted with ethyl acetate-hexane (1:3, volume  
30 ratio). A mixture of the obtained oily substance, 1N aqueous  
sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and  
ethanol (25 ml) was stirred at room temperature for 1 hour. 1N  
Hydrochloric acid (25 ml) was added, and the mixture was  
extracted with ethyl acetate. The ethyl acetate layer was  
35 washed with saturated aqueous sodium chloride solution, dried

(MgSO<sub>4</sub>) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give (2-{3-[1-(5-acetyl-2-pyridinyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (299 mg, yield 60%) as colorless  
5 crystals. melting point: 148-149°C.

【0307】

#### Example 333

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-1-propanol  
10 (500 mg), methyl (1-ethyl-3-hydroxy-1H-pyrazol-4-yl)acetate (297 mg), tributylphosphine (728  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (737 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected  
15 to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:5, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature  
20 for 1 hour. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and [1-ethyl-3-  
25 (3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1H-pyrazol-4-yl]acetic acid (520 mg, yield 72%) was obtained as amorphous from a fraction eluted with ethyl acetate-hexane (2:3, volume ratio).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.85 (6H, t, J = 7.2 Hz), 1.40 (3H, t, J =  
30 7.2 Hz), 1.60 - 1.83 (4H, m), 2.01 - 2.13 (2H, m), 2.52 - 2.67 (3H, m), 3.44 (2H, s), 3.96 (2H, q, J = 7.2 Hz), 4.21 - 4.28 (2H, m), 7.20 (1H, s), 7.90 - 7.96 (1H, m), 8.02 (1H, d, J = 8.4 Hz), 8.31 (1H, s), 8.56 - 8.60 (1H, m).

#### Example 334

35 To a mixture of 3-{3-butyl-1-[5-(trifluoromethyl)-2-

pyridinyl]-1H-pyrazol-4-yl]-1-propanol (500 mg), methyl (1-ethyl-3-hydroxy-1H-pyrazol-4-yl)acetate (310 mg), tributylphosphine (762  $\mu$ L) and tetrahydrofuran (100 ml) was added 1,1'-azodicarbonyldipiperidine (727 mg) at room  
5 temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a white solid was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained solid, 1N  
10 aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried  
15 ( $\text{MgSO}_4$ ) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-(3-{3-butyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}propoxy)-1-ethyl-1H-pyrazol-4-yl]acetic acid (403 mg, yield 55%) as colorless crystals. melting point: 109-110°C.

#### 20 **Example 335**

To a mixture of 3-{3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl]-1-propanol (500 mg), methyl (1-ethyl-3-hydroxy-1H-pyrazol-4-yl)acetate (322 mg), tributylphosphine (792  $\mu$ L) and tetrahydrofuran (100 ml) was  
25 added 1,1'-azodicarbonyldipiperidine (802 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane  
30 (1:3, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (25 ml), tetrahydrofuran (25 ml) and ethanol (25 ml) was stirred at room temperature for 1 hour. 1N Hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate  
35 layer was washed with saturated aqueous sodium chloride

solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained white solid was recrystallized from ethyl acetate-hexane to give [3-(3-(3-ethoxy-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl)propoxy)-1-ethyl-1H-pyrazol-4-yl]acetic acid (398 mg, yield 54%) as colorless crystals. melting point: 108-109°C.

【0308】

#### Example 336

To a mixture of 3-[1-(3,5-dichloro-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]-1-propanol (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (315 mg), tributylphosphine (645 mg) and tetrahydrofuran (60 ml) was added 1,1'-azodicarbonyldipiperidine (805 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated and isopropyl ether (20 ml) was added to the residue. The insoluble material was removed by filtration and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (3 ml), tetrahydrofuran (6 ml) and methanol (6 ml) was stirred at 50°C for 2 hours and poured into water. 2N Hydrochloric acid (3 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated. The obtained colorless crystals were collected by filtration to give (2-{3-[1-(3,5-dichloro-2-pyridyl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (550 mg, yield 72%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 105-106°C.

#### Example 337

To a mixture of 6-[4-(3-hydroxypropyl)-3-isopropyl-1H-pyrazol-1-yl]pyridazine-3-carbonitrile (500 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (430 mg), tributylphosphine (740 mg) and tetrahydrofuran (30 ml) was added 1,1'-

azodicarbonyldipiperidine (930 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a  
5 fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 2N hydrochloric acid (3 ml) and 1,4-dioxane (6 ml) was stirred while heating under reflux for 6 hours. Water (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was  
10 washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and (2-{3-[1-(6-cyanopyridazin-3-yl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-methoxyphenyl)acetic acid (300 mg, yield 37%) was obtained as  
15 colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 132-133.

#### **Example 338**

To a mixture of 2-[4-(3-hydroxypropyl)-3-isopropyl-1H-pyrazol-1-yl]pyrimidine-5-carbonitrile (330 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (280 mg), tributylphosphine  
20 (490 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (930 mg) at room temperature and the mixture was stirred overnight. The reaction solution was  
25 concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:3, volume ratio). A mixture of the obtained oily substance, 2N hydrochloric acid (3 ml) and 1,4-dioxane (6 ml) was stirred while heating under  
30 reflux for 6 hours. Water (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and (2-{3-[1-(5-cyanopyrimidin-2-yl)-3-isopropyl-1H-pyrazol-4-yl]propoxy}-3-  
35



methoxyphenyl)acetic acid (140 mg, yield 28%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (3:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 167-168.

5    **【0309】**

**Example 339**

To a mixture of 3-{3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (700 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (480 mg),  
10   tributylphosphine (820 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (1.03 g) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
15   obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (4 ml), tetrahydrofuran (6 ml) and methanol (6 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (4 ml) was added, and the  
20   mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (760 mg,  
25   yield 76%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 81-82.

**Example 340**

To a mixture of 3-{3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol  
30   (700 mg), methyl (2-hydroxy-3-methylphenyl)acetate (440 mg), tributylphosphine (820 mg) and tetrahydrofuran (50 ml) was added 1,1'-azodicarbonyldipiperidine (1.03 g) at room temperature and the mixture was stirred overnight. The  
35   reaction solution was concentrated. The residue was subjected

to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (4 ml), tetrahydrofuran (6 ml) and methanol (6 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (4 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [2-(3-{3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)-3-methylphenyl]acetic acid (730 mg, yield 73%). The crystals were recrystallized from ethyl acetate-hexane. melting point: 76-77.

**Example 341**

To a mixture of 3-{3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}-1-propanol (280 mg), methyl (3-ethyl-2-hydroxyphenyl)acetate (180 mg), tributylphosphine (330 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (410 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 1N aqueous sodium hydroxide solution (2 ml), tetrahydrofuran (4 ml) and methanol (4 ml) was stirred at room temperature for 5 hours. 1N Hydrochloric acid (2 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The obtained colorless crystals were collected by filtration to give [3-ethyl-2-(3-{3-(1-ethylpropyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]-1H-pyrazol-4-yl}propoxy)phenyl]acetic acid (250 mg, yield 60%). The crystals were recrystallized from ethyl acetate-hexane.

melting point: 93-94.

**[0310]**

**Example 342**

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-  
5 (trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}propanol (550 mg), methyl (2-hydroxy-3-methoxyphenyl)acetate (350 mg), tributylphosphine (710 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (930 mg) at room temperature and the mixture was stirred overnight. The  
10 reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was obtained from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). A mixture of the obtained oily substance, 2N hydrochloric acid (3 ml) and 1,4-dioxane (6 ml) was stirred  
15 while heating under reflux for 6 hours. Water (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and [2-(3-  
20 {3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}propoxy)-3-methoxyphenyl]acetic acid (180 mg, yield 22%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane.  
25 melting point: 163-164.

**Example 343**

To a mixture of 3-{3-(1-ethylpropyl)-1-[5-  
(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}propanol (610 mg), methyl (2-hydroxy-3-methylphenyl)acetate (360 mg),  
30 tributylphosphine (720 mg) and tetrahydrofuran (30 ml) was added 1,1'-azodicarbonyldipiperidine (900 mg) at room temperature and the mixture was stirred overnight. The reaction solution was concentrated. The residue was subjected to silica gel column chromatography, and a colorless oil was  
35 obtained from a fraction eluted with ethyl acetate-hexane

(1:4, volume ratio). A mixture of the obtained oily substance, 2N hydrochloric acid (3 ml) and 1,4-dioxane (6 ml) was stirred while heating under reflux for 6 hours. Water (20 ml) was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was subjected to silica gel column chromatography, and [2-(3-{3-(1-ethylpropyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]-1H-pyrazol-4-yl}propoxy)-3-methylphenyl]acetic acid (260 mg, yield 30%) was obtained as colorless crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). The crystals were recrystallized from ethyl acetate-hexane. melting point: 110-111.

**【0311】**

**15 Preparation Example 1 (Production of capsules)**

1) Compound of Example 1	30 mg
2) Finely divided cellulose	10 mg
3) Lactose	19 mg
4) Magnesium stearate	1 mg
20 Total	60 mg

1), 2), 3) and 4) are admixed and filled into a gelatin capsule.

**Preparation Example 2 (Production of tablets)**

25 1) Compound of Example 1	30 g
2) Lactose	50 g
3) Corn starch	15 g
4) Carboxymethylcellulose calcium	44 g
5) Magnesium stearate	1 g
30 1000 tablets	140 g

The whole amounts of 1), 2) and 3) and 30 g of 4) are kneaded together with water and the mixture, after vacuum drying, is granulated. The granular mixture is admixed with 14 g of 4) and 1 g of 5) and the resulting mixture is tableted using a tableting machine, to give 1000 tablets each

containing 30 mg of compound of Example 1.

**【0312】**

**【Effect of the Invention】**

5           The compound of the present invention is superior in a hypoglycemic action, a hypolipidemic action, a hypoinsulinemic action, insulin resistance-improving action, insulin sensitivity enhancing action and retinoid-related receptor function regulating activity, and can be used as an agent for  
10 the prophylaxis or treatment of diabetes (e.g., type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes mellitus); an agent for the prophylaxis or treatment of hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, hypo-high-density-lipoproteinemia,  
15 postprandial hyperlipemia); an agent for improving insulin resistance; an agent for enhancing insulin sensitivity; an agent for the prophylaxis or treatment of impaired glucose tolerance [IGT]; and an agent for preventing progress from impaired glucose tolerance to diabetes mellitus.

20

**【0313】**

**【sequence Listing】**

SEQUENCE LISTING

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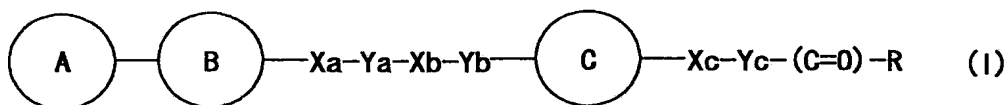


【Document】 Abstract

【Summary】

【Problem】 Provision of 1,2-azole derivative useful as a drug  
for the prophylaxis or prevention of diabetes mellitus and the  
5 like.

【Solving Means】 A compound represented by the formula



wherein ring A is a ring optionally having 1 to 3  
10 substituent(s);  
ring B is a 1,2-azole ring which may further have 1 to 3  
substituent(s);  
Xa, Xb and Xc are the same or different and each is a bond,  
-O-, -S- and the like;  
15 Ya is a divalent aliphatic hydrocarbon residue having 1 to 20  
carbon atom(s);  
Yb and Yc are the same or different and each is a bond or a  
divalent aliphatic hydrocarbon residue having 1 to 20 carbon  
atom(s);  
20 ring C is a monocyclic aromatic ring which may further have 1  
to 3 substituent(s); and  
R represents -OR<sup>4</sup> (R<sup>4</sup> is hydrogen atom or optionally  
substituted hydrocarbon group) and the like, or a salt thereof  
or a prodrug thereof.

25 【Main Drawing】 None